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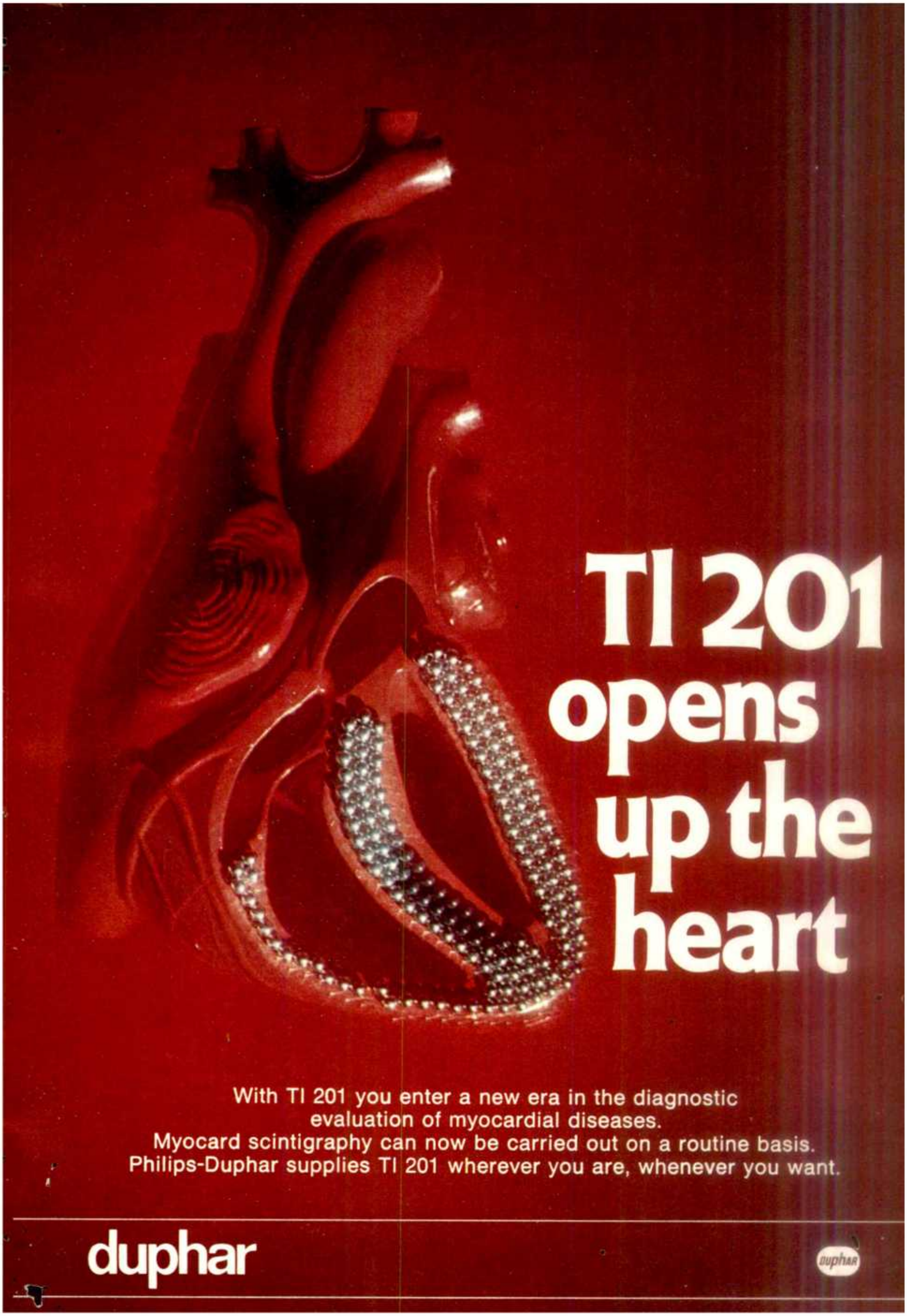

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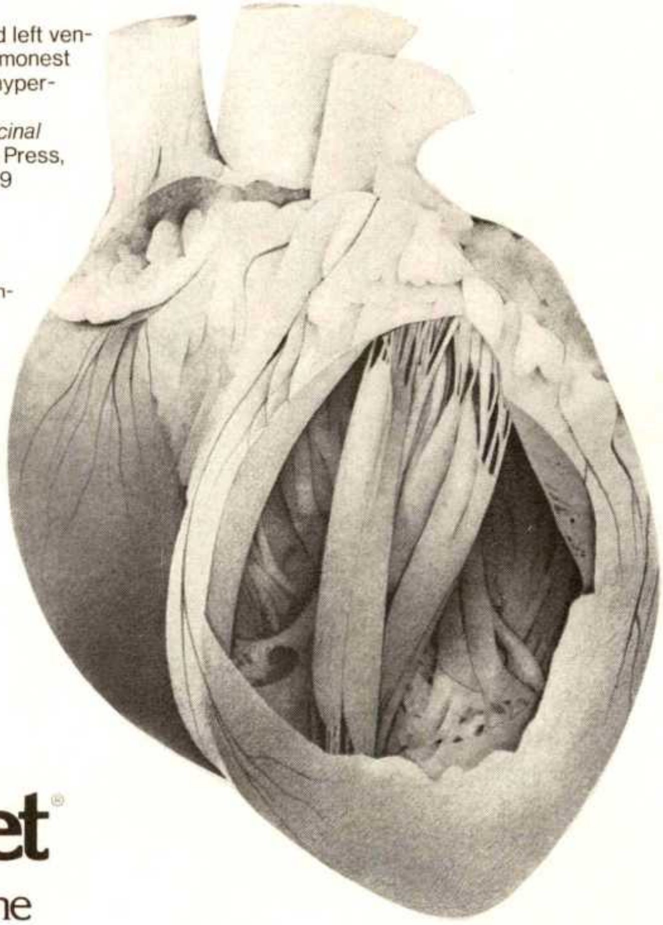

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Effect of environmental temperatures on oxygen consumption in infants with congenital disease of the heart

C. T. Kappagoda and F. J. Macartney[1]

From Cardiovascular Unit, University of Leeds; and Department of Paediatric Cardiology, Killingbeck Hospital, Leeds

The effect of changes in environmental temperature on the oxygen consumption in babies with congenital disease of the heart has been studied and it has been shown that an inverse relation exists between those two variables.

The significance of these findings on the practice of calculating systemic and pulmonary blood flow from predicted values of oxygen consumption is discussed.

There have been several studies on the influence of environmental temperature on oxygen consumption of normal and premature infants (e.g. Hey, 1969). There are, however, no comparable data on the effect of environmental temperature in infants with congenital diseases of the heart. The demonstration of such an effect would undoubtedly have considerable clinical significance because of its influence on the calculation of haemodynamic data. This paper presents the results of an investigation into this problem on a small sample of these infants.

Methods

This study was conducted on 6 babies with congenital defects of the heart and on 5 babies who were clinically normal. All the babies were investigated in the first month of life. The relevant clinical details are given in the Table. The babies were investigated while asleep in an incubator (Oxygenaire Mk III) approximately 1 hour after a feed. They were clothed in a nappy and a vest and no sedatives were administered.

The oxygen consumption was measured by an open circuit method which has been described in detail previously (Kappagoda and Linden, 1972; Kappagoda *et al.*, 1973). A Perspex hood was placed inside the incubator and positioned over the head of the patient. The hood was connected to the rest of the apparatus through the canopy of the incubator as shown in Fig. 1.

TABLE *Details of babies investigated*

Initials and sex of babies	*Age (wk)*	*Wt (kg)*	*Diagnosis*
Babies with congenital diseases of the heart			
C.C. (M)	2	3·2	Ebstein's anomaly
M.C. (M)	3	2·5	Tricuspid atresia and transposition
A.D. (F)	4	2·3	Coarctation of aorta
L.H. (M)	3	2·85	Tricuspid atresia and ventricular septal defect
C.T. (M)	3	2·5	Transposition
A.C. (F)	3	3·6	Transposition and persistent ductus arteriosus
Normal babies			
J.F. (M)	2	3·5	
J.A. (M)	2	3·2	
A.J. (F)	2	3·8	
J.B (F)	1	2·9	
M.W. (M)	1	4·0	

Air was drawn through the hood by means of the pump P (Type SA 37; Service Electronic Co. Ltd., Stanmore, Middlesex) and collected in the spirometer for a period of 45 s. The patient extracted oxygen from the stream of air as it passed through the hood. The gas collected in the spirometer was then pumped into a paramagnetic oxygen analyser (OA 137; Servomex Controls Ltd., Crowborough, Sussex) which was modified as described by Kappagoda and Linden (1972). The oxygen consumption was calculated as follows:

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*Received 7 July 1975.

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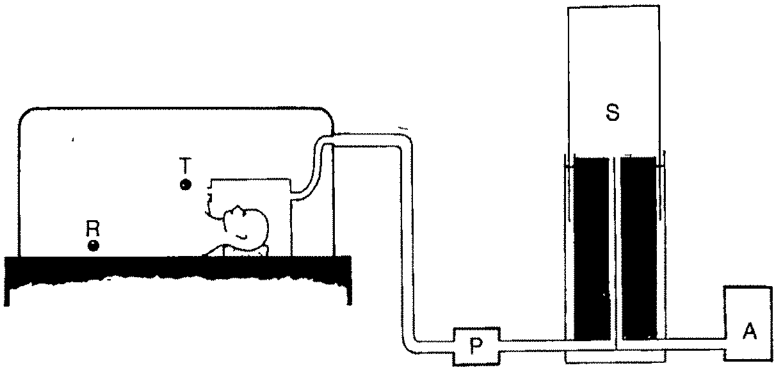

FIG. 1 *Diagram of apparatus. The baby lies on the mattress of the incubator. A hood is placed inside the canopy and positioned over the head. P—pump which draws a stream of air through the hood; S—spirometer; A—oxygen analyser; R and T denote telethermometers for recording rectal and environmental (i.e. incubator) temperatures, respectively.*

Volume of air drawn through the hood at STPD = V litre/min.

The concentration of oxygen in room air = X per cent.

The concentration of oxygen in the gas in the spirometer = Y per cent.

$$\text{The oxygen consumption} = V \times \left[\frac{X-Y}{100}\right] \text{ l/min STPD.}$$

During each investigation, the electrocardiogram, respirations, and the rectal temperature were monitored continuously (Kappagoda *et al.*, 1973). For the purpose of this study the environmental temperature was taken as the temperature measured 12·7 cm above the centre of of the platform of the incubator (British Standards Institution—as quoted by Hey and Mount, 1967). All the temperatures were measured using a telethermometer (Yellow Springs Instrument Corporation, Ohio).

Since this method of measuring oxygen consumption involved drawing a large volume of air (80–100 l/min) through the incubator, preliminary studies (not reported here) were undertaken which established that this method of measuring oxygen consumption did not result in changes in the 'environmental' temperature, i.e. temperature within the incubator. An example of this aspect of the study is shown in Fig. 2.

Experimental protocol

After each baby was comfortably settled and asleep in the incubator the oxygen consumption was measured four or five times at each of two or three environmental temperatures. Each baby was maintained at a given temperature for 25 to 45 minutes for 'equilibration' before the measurement of oxygen consumption. The humidity setting on the incubator was unchanged throughout the study. The range of temperatures over which the study was conducted was 23 to 31°C.

Both parents of each baby were consulted and their permission obtained before the investigation.

Results

All the babies were asleep during the study and the variations in environmental (i.e. incubator) temperatures were not accompanied by any significant changes in their rectal temperatures (< 0·5°C). The corresponding variations noted in the heart rates and respiratory rates were also relatively small, the largest variations recorded during the entire in-

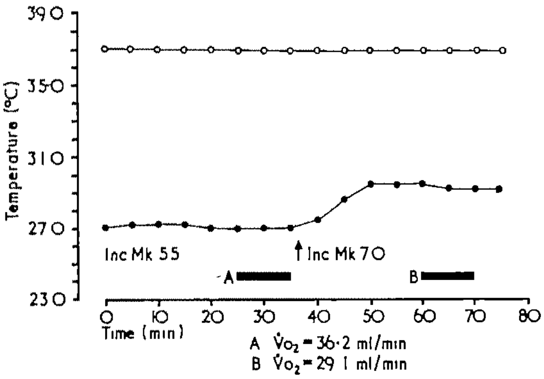

FIG. 2 *Effect of a change in environmental temperature on oxygen consumption in a child with congenital heart disease. Ordinate—environmental (i.e. incubator) temperature* ● *(°C) and rectal temperature* ○ *(°C). Abscissa—time (min). The bars (A and B) represent the periods over which the oxygen consumption* ($\dot{V}o_2$) *was measured. Note that there is no significant fluctuation in incubator temperature during the periods of measurement as compared with the control periods. Inc. Mk.: incubator setting.*

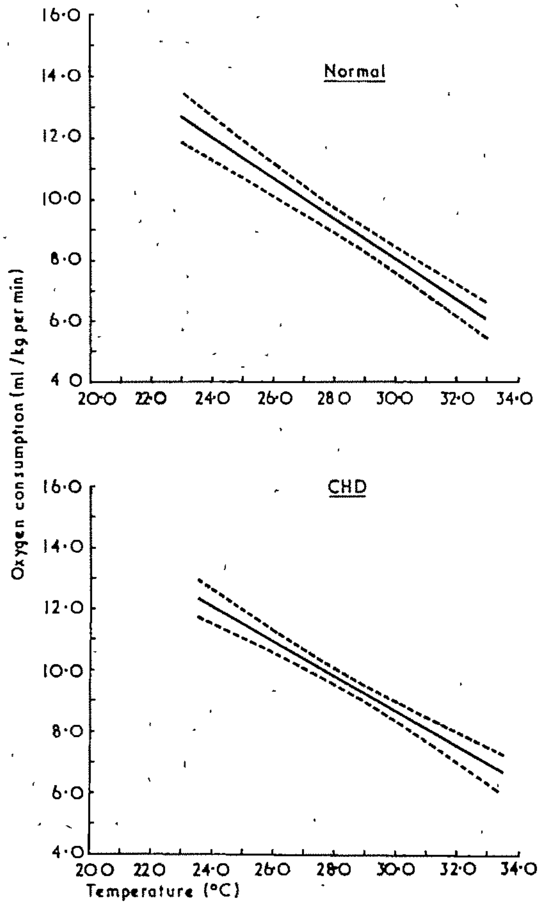

FIG. 3 *The relation between the oxygen consumption and the environmental temperature. Ordinate—oxygen consumption (ml/kg per min); abscissa—environmental temperature (°C). Top. Normal babies: The regression line is defined by the equation: Oxygen consumption = −0·66 × environmental temperature + 27·8. The interrupted lines are the confidence limits (R = 0·87: analysis based on 52 observations). Bottom. Babies with congenital defect of the heart. The regression line is defined by the equation: Oxygen consumption = −0·57 × environmental temperature + 25·7. The interrupted lines are the confidence limits (R = 0·89: analysis based on 58 observations).*

vestigation being 12 beats per minute for the former and 6 breaths per minute for the latter.

In all the babies investigated it was found that a reduction in the environmental temperature (i.e. incubator temperature) resulted in an increase in oxygen consumption. An example taken from a baby with congenital disease of the heart is illustrated in Fig. 2. The oxygen consumption measured at 27°C was 29·1 ml/min (mean of 4 observations; range 28·0–29·4) and that at 29·5°C was 36·2 ml/min (mean of 4 observations; range 34·9–37·7). It will be noted that the rectal temperature remained unchanged during the study and that the environmental temperature did not fluctuate significantly during the period of measurement, in spite of drawing 80 to 100 l/min of room air through the hood.

Since all the babies investigated showed a trend that was qualitatively similar to that indicated above, the results from individual babies in each group were pooled to yield two sets of data which were subsequently subjected to regression analyses (Fig. 3). In both groups significant inverse relations were demonstrated ($P < 0{\cdot}05$) between the oxygen consumption and the environmental temperature. The slopes of the two regression lines are not significantly different from each other ($P > 0{\cdot}05$). The adjusted means (Snedecor and Cochran, 1967) for the babies with congenital diseases of the heart are significantly greater ($P < 0{\cdot}05$) than in controls.

Discussion

The present investigation was undertaken to determine whether the oxygen consumption of infants with congenital diseases of the heart was related to the environmental temperature. Before considering the results of this study, it is necessary to examine the methods employed for the measurement of environmental temperature. The difficulties encountered in obtaining an accurate estimate of the true environmental temperature inside an incubator have been described in detail by Hey and Mount (1967). We are aware that the method used in this study for recording incubator temperatures would probably yield a value that would differ from that obtained by the more complex technique described by Hey and Mount (1967). However, in spite of this limitation, the present investigation has shown an inverse relation between the oxygen consumption and the environmental temperature in normal babies which is qualitatively similar to other published data (e.g. Adamsons, Gandy, and James, 1965; Hey, 1969). It must, therefore, be concluded that the methods employed in the present study are suitable for the purpose and that the relation demonstrated between oxygen consumption and the environmental temperature in the infants with congenital diseases of the heart is biologically valid.

These results have certain clinical implications. They bring into question the habit prevalent in many cardiac laboratories of predicting the oxygen consumption (for the purpose of calculating pulmonary and systemic blood flows) from tables (e.g. Rudolph and Cayler, 1958; LaFarge and Miettinen, 1970). It has already been shown in a study conducted under controlled laboratory conditions (Kappagoda *et al.*, 1973) that the predicted values for oxygen consumption have a random error which is at least seven times that of measuring it. The finding that the oxygen consumption is related to the environmental temperature suggests that haemodynamic data calculated from predicted values of oxygen consumption should be treated with the utmost caution, since their inherent random error may be compounded in babies, by a systematic error introduced by differences in environmental temperature between one laboratory and another.

There has also been some speculation in published reports about the existence of a state of relative 'hypermetabolism' in children with congenital diseases of the heart as compared with normal children (Lees *et al.*, 1965). In the context of the present investigation, this phenomenon would be revealed as a difference in the elevation of the two regression lines (Fig. 3), with the line for the babies with heart disease being above that of the control group, i.e. the adjusted means of the former would be significantly greater than that in the controls. Our investigation has indeed revealed such a statistical difference but much larger groups of infants would have to be studied before any biological significance could be attached to this observation.

The authors thank Dr. O. Scott and Dr. J. Buchanan for permission to study some of the patients under their care and the British Heart Foundation, Medical Research Council, and the Wellcome Trust for financial support.

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Ebstein's anomaly
Genetic study of 26 families

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The families of 26 patients with Ebstein's anomaly were examined. There were 120 first-degree relatives, 100 of whom were living, and 93 of these were examined. Information was available on 14 of the 20 who had died. No case of Ebstein's anomaly was found among the first-degree relatives, but 2 had ventricular septal defects and another, who died at 7 months, was said to have had congenital heart disease. In more distant relatives there were 6 with congenital heart disease, including 2 with ventricular septal defects and 2 with Fallot's tetralogy.

The tendency for congenital heart disease to occur in more than one member of a family has been recognized for many years (Polani and Campbell, 1955; Lamy, de Grouchy, and Schweisguth, 1957; Carleton, Abelmann, and Hancock, 1958).

Family studies have been undertaken in many of the common forms of isolated congenital heart disease. These include cardiomyopathy (Evans, 1949; Paré *et al.*, 1961; Barry and Hall, 1962; Emanuel, Withers, and O'Brien, 1971), persistent ductus arteriosus (Polani and Campbell, 1960; Wilkins, 1969), coarctation of the aorta (Campbell and Polani, 1961a), secundum atrial septal defect (Campbell and Polani, 1961b; Zuckerman *et al.*, 1962; Nora, McNamara, and Fraser, 1967; Williamson, 1969; Emanuel *et al.*, 1975), pulmonary stenosis (Campbell, 1962), situs inversus (Campbell, 1963), congenital aortic stenosis (Zoethout, Bonham-Carter, and Carter, 1964), ventricular septal defect (Campbell and Goodwin, 1965), atrioventricular defects (Emanuel *et al.*, 1968), transposition of great vessels and pulmonary atresia (Fuhrmann, 1968), and Fallot's tetralogy (Boon, Farmer, and Roberts, 1972), and it has been possible to quantitate genetic factors in both secundum atrial septal defects and atrioventricular defects.

The familial incidence of Ebstein's anomaly has not been studied though more than one case in a single family has been reported on several occasions. Gueron *et al.* (1966) reported a 20-year-old man with Ebstein's anomaly who died of cardiac failure, and a 12-year-old sister similarly affected. Both diagnoses were confirmed at necropsy. Donegan *et al.* (1968) reported a 6-year-old boy with a 29-year-old maternal uncle with Ebstein's anomaly, in both of whom the diagnosis was confirmed by cardiac catheterization without angiography. Simcha and Bonham-Carter (1971) noted 2 families: in one a father and daughter, and in the other 2 brothers were affected, but no investigations were reported; and Watson (1974), in his assembled series of 505 cases, found another family in which 2 sisters were diagnosed clinically as having Ebstein's anomaly.

The present study was undertaken to assess the familial incidence of Ebstein's anomaly and to determine the frequency of other congenital cardiac defects in the first-degree relatives. In view of the frequent association of Ebstein's anomaly and secundum atrial septal defect in individual cases, the presence or absence of atrial septal defects in the first degree relatives was of particular interest.

Subjects and methods

Data on the propositi and first-degree relatives were collected as in previous studies (Emanuel *et al.*, 1968, 1971,1975). There were 26 propositi from the National Heart Hospital, The Middlesex Hospital, and The Hospital for Sick Children. Clinically, all had the classical features of Ebstein's anomaly. In 9 the diagnosis was confirmed by cardiac catheterization and angiocardiography and in 2 by cardiac catheterization alone. In a further 11 the anatomy was examined at either operation (5) or necropsy (6). The remaining 4 propositi were not investigated, but accepted on clinical

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grounds. The age range was 5 to 65 years, with a mean of 17·6 years.

There were 65 siblings, 51 of whom were living and 14 dead. Forty-six of the living siblings were examined and this included a chest radiograph and an electrocardiogram. Diagnostic information was available on 10 of the 14 who had died, Of the 52 parents, 46 were living and of these 44 were similarly examined. Six had died and diagnostic information was available on 4. There were 3 children, and all were examined. Diagnostic information was, therefore, available on 107 (89%) of the 120 first-degree relatives.

Results

None of the first-degree relatives had Ebstein's anomaly, but ventricular septal defects were present in one sibling and one child. Another sibling, who died in infancy, was said to have had congenital heart disease, but no further information was available.

In more distant relatives, a ventricular septal defect was present in 2, in one of whom the diagnosis was confirmed at necropsy and in the other by cardiac catheterization and angiocardiography. A further 2 relatives had Fallot's tetralogy which was surgically corrected in both. Two other relatives may also have had congenital heart disease but neither was investigated (Table).

There was no incidence of consanguinity between the parents. Information relating to pregnancy was obtained from all 26 mothers; 108 pregnancies were reported, 15 (13·8%) of which ended in miscarriages. In addition there were 2 stillbirths. These figures are well within the accepted range quoted by Logan (1959).

Conclusion

There was no evidence of a familial incidence of Ebstein's anomaly in these 26 families, and no relative with an isolated secundum atrial septal defect. The frequency of congenital heart disease in first-degree relatives was considerably higher at 2·8 per cent (3 out of 107) than in the general population, 0·05–0·07 per cent (Carlgren, 1959; McKeown and Record, 1960; Mustacchi, Sherins, and Miller, 1963; Smithells, 1968). This finding was in keeping with the results from other family studies of isolated congenital heart disease.

The frequency of ventricular septal defects in these families, either as a simple lesion (4 cases) or as part of Fallot's tetralogy (2 cases) was noted, but no embryological explanation for this association could be found.

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TABLE *Congenital heart disease in 9 affected relatives*

	Relationship and sex	*Diagnosis*	*Method or source of diagnosis*
	First degree		
1.	Sibling (M)	Ventricular septal defect	Clinical*
2.	Sibling (F)	'Congenital heart disease'	Death certificate (died at 7 months)
3.	Child (M)	Ventricular septal defect	Cardiac catheterization and angiocardiography
	Second degree		
4.	Niece	Ventricular septal defect	Cardiac catheterization and angiocardiography
5.	Maternal uncle	'Congenital heart disease'	Death certificate (died at 6 months)
	Third degree		
6.	First cousin (M)	Ventricular septal defect	Necropsy
7.	First cousin (M)	Pulmonary valve stenosis	Clinical*
	Others		
8.	(M)	Fallot's tetralogy	Surgery
9.	(M)	Fallot's tetralogy	Surgery

*Clinical investigations = physical examination, electrocardiography, and a chest radiograph but excludes haemodynamic investigations.

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Assessment of left ventricular systolic function in man from simultaneous echocardiographic and pressure measurements

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Simultaneous measurements of left ventricular dimension and wall thickness by echocardiography, and of pressure by micromanometer, were made at cardiac catheterization in 30 patients with heart disease, in order to study mechanisms of impairment of left ventricular systolic function. Echocardiograms and pressure traces were digitized so that continuous measurements of left ventricular wall thickness and dimensions with their rates of change could be obtained. Ejection fraction was estimated from digitized cineangiograms.

In all patients, except those with severe mitral regurgitation, there was close correlation ($r=0\cdot92$) between peak left ventricular dP/dt and peak rate of reduction of dimension. Myocardial power values, calculated as the product of circumferential shortening rates and wall stress were plotted throughout the cardiac cycle, and peak values in patients with normal left ventricular function were in the range 30 to 60 mW cm^{-3} myocardium. Pressure-dimension loops were constructed, which reflected the relation between the function of a localized region of cavity studied by echocardiography and that of the ventricle as a whole in the pressure wave form. Incoordinate contraction was associated with distortion of the loop and a reduction in its area to less than 75 per cent that of the maximum for the cycle in question (cycle efficiency).

In patients with left ventricular disease, ejection fraction, peak power, and cycle efficiency were all reduced, either singly or in combination. There was no consistent pattern, however, suggesting that clinical left ventricular disease may be the resultant of a number of different types of disturbance. These include structural abnormalities, reduction in peak rates of myocardial shortening or power development, and incoordinate contraction. The present investigation suggests ways in which these may be separated and studied in individual patients.

Echocardiography can be used to study left ventricular function in a number of ways. Measurements of cavity dimensions can be used to estimate left ventricular volumes and thus ejection fraction (Fortuin *et al.*, 1970; Pombo, Troy, and Russell, 1971; Feigenbaum *et al.*, 1972). More recently, a second index of ventricular performance, the mean velocity of circumferential fibre shortening, has been derived from simultaneous measurements of cavity size and ejection time, and shown to correlate with other indices of contraction pattern (Paraskos *et al.*, 1971; Cooper *et al.*, 1972). Further information about time-dependent aspects of ventricular contraction may be obtained from continuous measurements of rates of wall movement, using simple digitizing techniques (Gibson and Brown, 1973). Finally, it is possible that echocardiography might be used to demonstrate incoordinate contraction, which has been shown to be a significant abnormality in patients with valvular heart disease and cardiomyopathy (McDonald, 1972; Kreulen, Gorlin, and Herman, 1973), as well as those with ischaemic heart disease.

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It was the purpose of the present study to extend the use of echocardiographic methods in assessing the degree to which these different mechanisms, either separately, or in combination, interfered with left ventricular performance in patients with heart disease. The function of myocardium in a single region of the ventricle was described in terms of work and power production, from simultaneous estimates of left ventricular pressure, diameter, and wall thickness. These measurements of local function were then related to that of the ventricle as a whole in order to assess the extent to which incoordinate contraction was present.

Methods

In systole, the rate at which the myocardium does external work, i.e. the power that it generates, is given by the product of developed force and shortening rate. Measurement of power in the intact heart is complex, since values of developed force and shortening rate may vary, not only at the same time in different parts of the ventricle, but also throughout the cardiac cycle in the same region. If such calculations are to be made, therefore, they must be based on continuous measurements of pressure, wall thickness, and local curvature throughout the cycle, and the results are only applicable to the region of the left ventricle for which measurements are made. Estimates of myocardial work which is the time integral of power, and represented by the area under the graph of power development against time, are subject to the same limitation, since wall forces and shortening rate cannot be assumed to remain constant as ventricular size and shape change throughout systole.

In the present investigation, power production was calculated for the region of posterior wall of the left ventricle studied by echocardiography. It was assumed that this area lay in the equatorial region of an ellipsoid of finite wall thickness, whose long axis was identical with that of the left ventricle. Using the method of Falsetti *et al.* (1970), mean circumferential stress was derived for an annulus of myocardium perpendicular to the long axis of the ellipsoid, which was assumed to be circular in cross-section, with an internal diameter equal to the echocardiographic dimension. We had no direct information about longitudinal forces, and though they are of a similar order of magnitude to circumferential ones, we did not consider them, while shear forces were assumed to be small and were neglected. The long axis of the ellipsoid was predicted from the echocardiographic dimension using regression equations derived from a previous study (Gibson, 1973). The average circumferential stress is given by:

$$\sigma=\frac{0{\cdot}34\,\mathrm{PM}}{\mathrm{W}}\;\frac{(2\mathrm{L}^2-\mathrm{M}^2)}{(\mathrm{L}^2+\mathrm{MW})}$$

where P = ventricular pressure (mm Hg), L = major axis, M = minor axis, and W = wall thickness (cm). Stresses are referred to a position in the mid-wall, so that the circumference at this point was given by $\pi(\mathrm{M}+\mathrm{W})$, and the shortening rate as its first differential with respect to time. Values were normalized to refer to a cubic centimetre of myocardium at end-diastole, and are thus 'fiber corrected' in the sense of Falsetti *et al.* (1970). Estimates of power production as the product of circumferential stress and shortening rate do not include longitudinal components.

The physiological value of local power production by the myocardium depends on the extent to which it can be translated into useful work on the circulation. A full description of myocardial performance in any particular region must thus contain an index of the relation between local and overall ventricular function, and in particular, of the phase relation between the two. In the present study, this was realized by constructing pressure dimension loops. Regional behaviour is reflected in the echocardiographic dimension, while that of the ventricle as a whole is implicit in the pressure waveform. Simple pump theory indicates that the amount of useful energy transferred from the myocardium to the circulation per unit area of endocardium is given by:

$$\oint \mathrm{PdD}$$

where P = instantaneous left ventricular pressure and D = instantaneous dimension. This function has a maximum value when the loop is rectangular, when the area is given by the product of the total pressure and dimension changes for the cardiac cycle in question. If the loop has any other configuration, then its area will be less. We have, therefore, defined cycle efficiency as the ratio of loop area to that of the rectangle that just encloses it, i.e. the ratio of observed external work to the maximum possible for a ventricle working over the same range of pressure and dimension.

Patients

Thirty patients were studied, who required right and left heart catherization for diagnostic purposes. In all of them it was possible to record technically satisfactory echocardiograms of the left ventricular cavity and to pass a No. 5 catheter across the aortic valve. Patients with ischaemic heart disease were deliberately excluded. The nature and purpose of the investigation were explained to the patients, and their consent was obtained. In no case did the study add more than 15 minutes to the cardiac catheterization and there were no complications.

The patients were divided into two groups. Group 1 were those in whom values of end-diastolic pressure, peak left ventricular dP/dt, and ejection fraction were normal, and in whom there was no lesion which might have been expected to increase the pressure of volume load of the left ventricle, or to cause localized or generalized myocardial disease. It is recognized, however, that these patients were not normal, and that minor impairment of left ventricular function might have been present. Group 2 consisted of patients with left ventricular disease whose clinical details are given in Table 1.

Cardiac catheterization

The patients were studied fasting and supine, and were premedicated one hour before the start of the procedure with 200 mg amylobarbitone given orally. Left ventricular pressures were measured with a Millar micromanometer inserted through a right brachial arteriotomy and were recorded photographically at a paper speed of 100 mm/s using an SE 3012 ultraviolet recorder. Zero for these pressure measurements was taken as atmospheric, and a simultaneous electrocardiogram was recorded along with an echocardiogram. When these measurements had been completed, an angiographic catheter was substituted, and left ventriculography performed with the patient in the anteroposterior or right

TABLE 1 *Clinical details*

Case No.	*Diagnosis*	*Surface area (m²)*	*Sex age*	*Ejection fraction (%)*	*Left ventricular pressure*		
					Peak (mm Hg)	*ED (mm Hg)*	*Peak dP/dt (mm Hg/s)*
Group 1							
1	Mild mitral stenosis	1·8	M51	75	170	10	1680
2	Roget VSD	0 73	M5	75	148	7	3460
3	Mild mitral stenosis	1·8	F54	65	136	4	1800
4	Secundum ASD	1·6	M25	72	117	8	1540
5	Mild pulmonary stenosis	1·8	F19	72	132	8	1970
	Mean	1·55	30	72	140	7·4	2090
	SD	0·46	21	4	20	2·2	780
Group 2							
6	Mixed mitral valve disease	1·6	F36	65	100	8	1300
7	Aortic regurgitation	1·9	M39	30	110	25	700
8	Mitral stenosis	1·5	F39	46	120	15	1460
9	Mitral stenosis and regurgitation	1·9	M67	46	124	5	1127
10	Mitral stenosis and hypertension	1·8	M58	54	104	4	1440
11	Ruptured chordae tendineae	1·6	M67	39	134	20	1630
12	Mitral stenosis and regurgitation	1·5	M23	40	81	0	1440
13	Mitral stenosis and regurgitation	1·7	M35	60	90	8	1720
14	Mitral and aortic regurgitation	2·1	M48	70	105	12	820
15	Ruptured chordae tendineae	1·9	M27	81	122	9	1720
16	Mitral and aortic regurgitation	1·5	F15	51	180	35	1900
17	Mitral stenosis: cardiomyopathy	1·7	M51	29	100	5	1160
18	HOCM	1·5	M23	64	124	8	1200
19	Aortic regurgitation	1 6	M17	82	120	5	1750
20	Mitral regurgitation	1·5	F60	58	128	5	1300
21	Aortic and mitral regurgitation	1·5	F20	70	127	25	1500
22	Mitral regurgitation	1 8	F16	80	160	5	2280
23	Mitral regurgitation	1·9	M60	80	137	15	1390
24	Mitral and aortic regurgitation	0·9	F 7	65	132	18	1590
25	Aortic stenosis	2·1	M26	78	180	6	2200
26	Mitral stenosis	1·7	M42	22	100	10	1370
27	Ruptured chordae tendineae	2·0	M68	79	120	16	1500
28	Aortic regurgitation	1 7	M39	34	170	35	1070
29	Mitral Starr	1·8	F61	65	140	15	2470
30	Ruptured chordae tendineae	1·9	M30	64	150	22	1350
	Mean	1·7	39	55	126	13	1495
	SD	0·25	19	20	26	9·4	420

VSD=Ventricular septal defect: ASD=Atrial septal defect: HOCM=Hypertrophic obstructive cardiomyopathy.
Conversion factor to SI units: 1mm Hg≈0·133 kPa.

anterior oblique position. Cine film was exposed at 50 frames per s, and calibration was by means of a grid at mid-chest level.

Echocardiographic techniques

At the same time as left ventricular pressure was being measured, the left ventricular dimension was recorded on Polaroid film using an Ekoline 20 ultrasonoscope with a 2·25 MHz transducer, and posterior wall thickness measured by the method of Sjogren, Hytonen, and Frick (1970). Clear continuous endocardial echoes, which were distinguished from those originating from the mitral valve, were recorded throughout the cardiac cycle in all cases. An identical electrocardiogram to that recorded with the pressure trace was superimposed on all records, and during exposure, a 1 mV calibration signal was recorded on both, enabling the two to be correlated, and data from the same beat to be unequivocally identified on both records.

Digitization

Echocardiograms and pressure traces were digitized using methods that have previously been described (Gibson and Brown, 1974). Left ventriculograms were also digitized, and cavity area calculated for each frame of a single beat (Gibson and Brown, 1975). Ventricular volume estimates were derived from cavity area, and ejection fraction derived as stroke volume divided by end-diastolic volume. From digitized data, plots were made of left ventricular pressure, wall thickness, and dimension (D) throughout the cardiac cycle (Fig. 1). The first derivatives of dimension (dD/dt), pressure, and normalized left ventricular dimension (1/D.dD/dt) with respect to time, were also plotted. Left ventricular

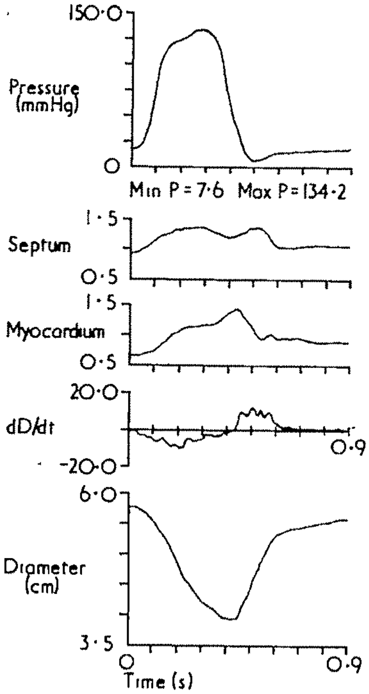

FIG. 1 *Computer output showing from above down measurements of left ventricular pressure, septal and wall thickness, the rate of change of dimension and the dimension.*

wall stress, power, work, and cycle efficiency were calculated as described above. In patients in sinus rhythm, mean values from at least two beats were taken. In those in atrial fibrillation, mean values for up to 6 beats are given in Tables 1 and 2, while in Fig. 2, 3, and 9, values from individual beats are shown.

Results

Left ventricular dimension

The mean end-diastolic dimension in the group of patients with normal left ventricular function was 4·0 cm, dropping to 2·5 cm at end-systole. The peak rate of change of dimension was 7·8 cm/s, or 2·5 s^{-1} when normalized to unit length. In patients with left ventricular disease, mean values of both end-systolic and end-diastolic dimension were greater, being 4·1 and 5·6, respectively, while the peak rate of change of dimension was 8·3 cm/s or 1·95 s^{-1}. These results are given in detail in Table 2.

Peak rate of rise of left ventricular pressure

This had a mean value of 2090 mm Hg/s (278 kPa/s) in the normal patients and of 1495 mm Hg/s (199 kPa/s) in those with left ventricular disease (Table 1). There was highly significant correlation between peak rates of rise of pressure and peak rate of reduction in dimension in the same beat, in patients without significant mitral regurgitation (Fig. 2) the regression equation being:

(Peak dP/dt)=730 (Peak 1/D. dD/dt)+320 mm Hg/s (42·5 kPa/s),
standard error of estimate 280 mm Hg/s (37·2 kPa/s), r=0·92.

The effect of mitral regurgitation was that peak rates of wall movement were associated with lower values of peak rate of rise of pressure than would be predicted from the regression equation (Fig. 3).

Left ventricular wall stress

Peak left ventricular circumferential wall stress was 320 g cm^{-2} in the normal group and 344 g cm^{-2} in those with left ventricular disease. Considerable scatter was present in the latter group, with values ranging from 140 g cm^{-2} in 2 patients with hypertrophic cardiomyopathy and aortic stenosis, to values greater than 500 g cm^{-2} in patients with large ventricular cavities caused by valvular regurgitation.

Left ventricular power and work

The mean value of peak myocardial power recorded in the normal group was 46 mW cm^{-3}. In patients with left ventricular disease, this was reduced to 25 mW cm^{-3}, and in addition, significant negative values were present in late systole (Fig. 4 and 5). Myocardial work, derived as the time integral of power, had a mean value of 4·5 mJ cm^{-3} per beat in the normal group and of 3·2 mJ cm^{-3} per beat in those with left ventricular disease. This latter value was derived from a mean positive value of 3·7 mJ cm^{3} per beat and a negative one of 0·55 mJ cm^{-3} per beat.

Pressure-dimension relations

A representative pressure-dimension loop from a patient in the normal group is shown in Fig. 6. It is almost rectangular in form, and has a cycle efficiency of 88 per cent. The mean value in the normal group was 83 per cent. A loop from a patient with severe mitral regurgitation but good left ventricular function is shown in Fig. 7. Distorted loops appeared in the presence of left ventricular disease (Fig. 8), with dimension changes occurring during the periods of maximum rate of change of pressure during contraction and relaxation. In patients in sinus rhythm, beat to beat reproducibility was demonstrated by a root mean square difference of 3 per cent between duplicate deter-

TABLE 2

	Diameter				*Power*		*Work*	
Case No.	*ED (cm)*	*ES (cm)*	*ED Wall thickness (cm)*	*Peak stress (g cm^{-2})*	*Positive (mW cm^{-3})*	*Negative (mW cm^{-3})*	*Positive (mJ cm^{-3})*	*Negative (mJ cm^{-3})*
Normal LV function—Group 1								
1	5·0	3·1	1·0	400	40	0	3·9	0
2	3·6	2·1	0·7	400	65	0	6·7	0
3	4·0	2·5	0·9	250	35	0	3·6	0
4	3·6	2·6	0·8	240	30	0	2·3	0
5	3·6	2·0	0·7	320	60	0	5·8	0
Mean	4·0	2·5	0·82	320	46	0	4·5	0
SD	0·61	0·44	0·13	78	16	0	1·8	0
Impaired LV function—Group 2								
6	5·6	4·2	0·9	220	20	0	2·3	0·06
7	8·6	7·7	1·4	350	17	17	2·0	1·1
8	5·0	4·2	0·6	500	26	3	2·5	0·9
9	5·1	4·2	0·9	300	16	11	3·7	0·2
10	3·8	2·3	0·8	280	20	3	2·4	0·3
11	5·8	3·9	0·8	400	30	0	4·6	0·7
12	4·4	3·6	0·8	260	15	5	3·9	0·2
13	6·6	5·1	1·2	230	10	0	1·3	0·1
14	7·0	5·3	1·2	250	18	18	3·5	1·4
15	6·9	5·0	0·8	500	37	0	4·3	0·2
16	5·6	4·0	1·0	620	45	5	5·9	1·5
17	6·0	5·2	1·2	200	10	0	1·4	0·2
18	3·2	1·8	1·1	140	9	0	0·8	0·3
19	4·1	3·0	0·6	360	25	0	4·3	0·5
20	7·4	5·5	1·1	350	10	0	2·9	0·1
21	6·1	4·2	1·1	380	35	15	9·2	1·0
22	4·0	2·5	1·3	200	29	0	5·1	0·2
23	5·2	2·7	0·8	200	18	0	3·6	0·6
24	6·0	4·3	0·7	500	43	0	5·2	0·6
25	3·3	1·9	2·0	140	15	0	2·0	0·3
26	6·2	5·4	0·9	280	30	0	0·8	0·30
27	5·0	2·8	0·9	300	25	0	3·1	0·5
28	8·5	7·3	1·0	750	25	0	4·7	0·5
29	5·0	3·2	0·9	340	35	0	4·2	0·9
30	6·1	3·7	0·8	490	50	0	9·2	1·1
Mean	5·6	4·1	0·98	344	25	4	3·7	0·55
SD	1·4	1·5	0·29	150	11	5·7	2·2	0·43

minations on successive beats. In the presence of atrial fibrillation, however, distinct beat-to-beat changes occurred, apparently dependent on pulse interval, beats in which peak left ventricular pressure and its rate of change were low were associated with low or even negative cycle efficiency, implying aneurysmal behaviour of the region being studied. When results from all the patients were considered there was a non-linear relation between cycle efficiency and peak left ventricular dP/dt (Fig. 9).

Discussion

Several methods have been used to assess left ventricular function in patients with heart disease. Ejection fraction, which has been widely used both to document inotropic effects and to compare patients with one another, is determined as the ratio of stroke volume to end-diastolic volume, and is, therefore, dimensionless (Bristow *et al.*, 1964; Miller and Swan, 1964; Wilcken, 1965). A second group of measurements are time-related, derived either from the rate of rise of pressure or rate of change of dimension (Gault, Ross, and Braunwald, 1968), and may be expressed either directly or in normalized form. They are based on the experimental observation that tension is developed more rapidly, and that at constant load, the rate of shortening is greater after the application of a positive inotropic stimulus (Sonnenblick, 1962). A close relation between measurements of peak

Net (mJ/cm³)	*Cycle efficiency (%)*	*Peak dD/dt (cm/s)*	*Normalized peak dD/dt (s^{-1})*
3·9	78	5·6	1·9
6·7	82	11 0	3·7
3 6	88	11·5	3 0
2·3	83	8·0	2·5
5·8	83	8·0	2·5
4·5	83	7·8	2 5
1·8	3·6	3 6	0·87
2·2	62	5·1	1·0
0·86	43	4 0	0·65
1·6	78	6·7	1 1
3·5	70	4·9	1·0
2·1	82	9·3	3·7
3 9	71	7·7	1·8
3·7	80	6·9	1·8
1 2	83	10·0	1·9
2 1	49	8·0	1·2
4·1	77	17·0	2·3
4·4	79	9·5	2·0
1·2	76	5 0	1·0
0 5	59	7·0	3·5
3·8	85	6·0	1·8
2·8	85	9·0	1·8
8·2	70	7·3	1·7
4·9	85	8·0	3·0
3·0	88	10·0	3·2
4·6	85	10·0	1·9
1·7	74	7·0	2 6
0·5	71	4 5	0·8
2·6	76	12 0	2·6
4·2	78	5 0	0·9
3 3	71	11·5	2·6
8 0	85	13·0	2·8
3·2	75	8·3	1·95
2·0	11	3·1	0·98

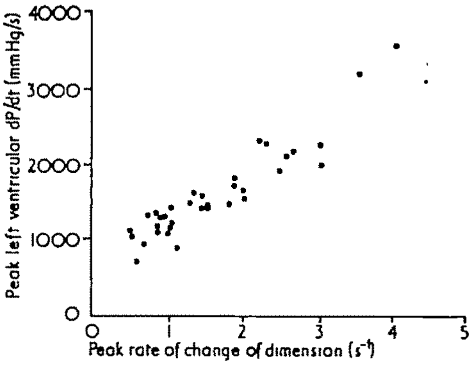

FIG. 2 *Relation between peak rates of change of left ventricular pressure and of dimension for patients without significant mitral regurgitation. Each point represents values from a single beat.*

rate of change of pressure and of dimension has previously been described in dogs (Barnes *et al.*, 1973), and was confirmed in the present study. It may have a potential application in the non-invasive assessment of left ventricular function and requires further evaluation. It did not apply, however, in patients with significant mitral regurgitation, when peak values of left ventricular dP/dt were lower than would be predicted from those of peak rate of wall movement, demonstrating the influence of after-load on such time-dependent variables. This additional effect may be taken into consideration by combining estimates of circumferential shortening rate with those of wall stress derived from measurements of cavity pressure, diameter, and wall thickness to calculate myocardial power and work. The only significant geometrical assumption required is that the cavity is approximately circular at the site at which measurements are made. This method of calculation of stroke work has the limitations that only the circumferential components are assessed, and that the results are strictly applicable only to the area of myocardium for which they are derived. However, it has the potential advantage over other methods of calculating stroke work, for example, as the

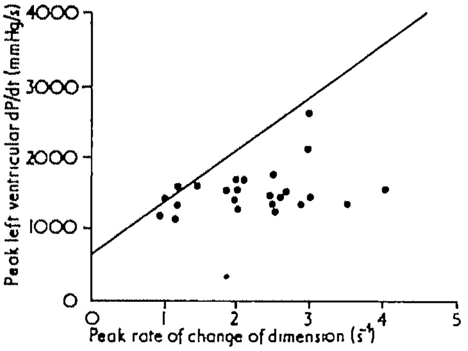

FIG. 3 *Relation between peak rates of change of pressure and dimension from patients with significant mitral regurgitation. Each point represents values from a single beat. The regression line derived from the points in Fig. 2 relating to patients without significant regurgitation is superimposed.*

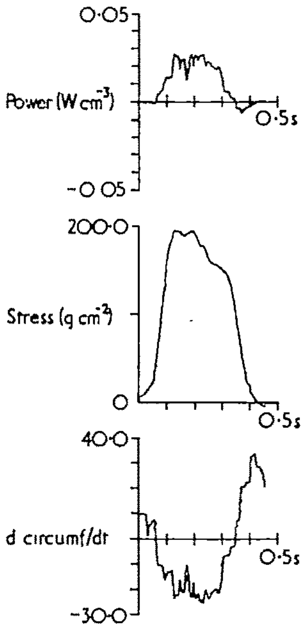

FIG. 4 *Changes in mid-wall circumferential shortening rate, wall stress, and power from a patient with good left ventricular function (Case 22).*

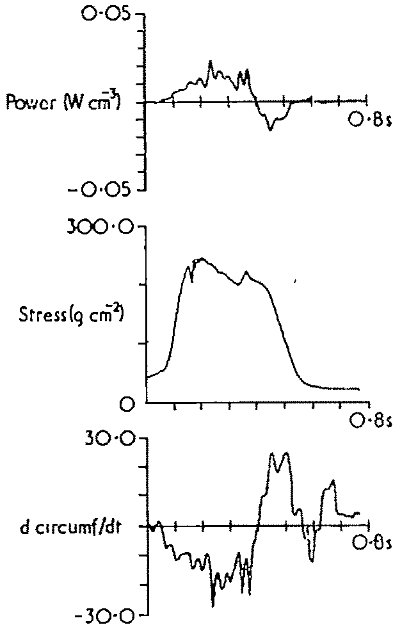

FIG. 5 *Changes in mid-wall circumferential shortening rate, wall stress, and power in a patient with impaired left ventricular function. Peak power is reduced, and a negative component is apparent in late systole (Case 14).*

product of stroke volume and ejection pressure, that changes in cavity dimension and wall thickness are taken into account, and that the results can be considered to a large extent independent of ventricular geometry.

The pattern of power production was uniform in the patients with normal left ventricular function judged clinically, haemodynamically, and angiocardiographically. Maximum values tended to be recorded early in systole, and fell as cavity size and wall stress dropped during ejection. Peak values were in the range 30–60 mW cm^{-3} myocardium, while total stroke work had a mean value of 4·5 mJ cm^{-3} per beat. Negative values of power were recorded during diastole, but these were very small because wall stress was low so that the effect of this diastolic component on overall stroke work was negligible. In the presence of left ventricular disease, this pattern of power development was modified in at least 2 ways. In some patients, particularly those in whom cavity size was large, peak power was reduced indicating that the effect of cavity dilatation in increasing wall stress was more than offset by the concomitant reduction in peak rates of wall movement. This might be anticipated, since at constant pressure, wall tension increases linearly with the diameter of the ventricle, whereas, for any given ejection rate, the peak rate of wall movement varies inversely as the square of the diameter. A more consistent finding in patients with left ventricular disease was the presence of negative power components, particularly in late systole, reflecting outward wall movement at a time when ventricular pressure was still raised. This resulted in stroke work, calculated as the time integral of power, being reduced even when peak power values were within the normal range.

The pattern of left ventricular contraction was also examined by constructing pressure-dimension loops. These have previously been derived in man from pressure and echocardiographic data (Gibson, 1972; McLaurin *et al.*, 1973), but have been interpreted as though they represented pressure-volume relations. The echocardiographic dimension, however, represents function in only a small region of the cavity, and so it is potentially affected by shape changes occurring in isovolumic contraction or relaxation. Pressure-dimension relations, unlike those between pressure and volume, thus allow the timing of over-all ventricular function as reflected in the pressure trace to be compared with contraction in the localized area represented by the echo

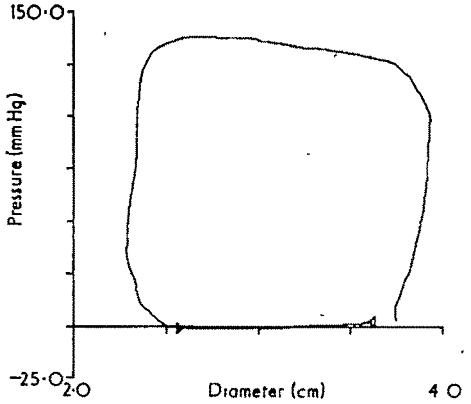

FIG. 6 *Pressure-dimension loop from a patient with normal left ventricular function (Case 3).*

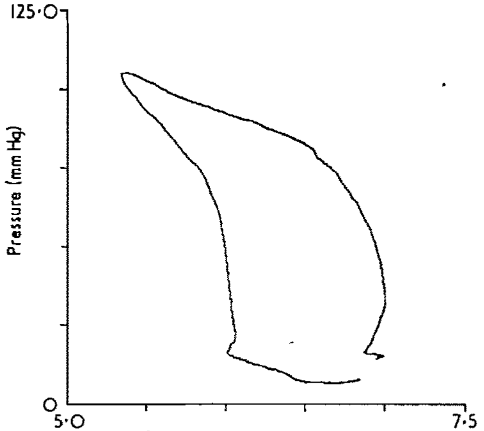

FIG. 8 *Pressure-dimension loop from a patient with aortic regurgitation and poor left ventricular function (Case 14).*

dimension (Rushmer, 1956b; Gibson and Brown, 1973; Tyberg *et al.*, 1973). Disorganized contraction, represented by loss of the optimal relation between the two, is reflected in a reduction in mechanical efficiency, i.e. in the ratio of observed external work to the maximum possible for a ventricle working over the same range of pressure and dimension. In patients with normal left ventricular function, cycle efficiency was high, as might have been anticipated from simple mechanical considerations. Mitral regurgitation modified the shape of the loop by causing reduction in dimension in what would normally have been in the phase of isovolumic contraction, while aortic regurgitation was associated with an increase in dimension in the early relaxation phase. The magnitude of these effects depends on the relative rates of change of pressure and dimension in early and late systole, and shows that in patients with valvular regurgitation, unlike those without, reduced efficiency of energy transfer from the myocardium to the circulation may result from prolongation of the initial phases of contraction or relaxation. When left ventricular function was normal, these effects were small in spite of severe regurgitation (Fig. 7). The main factor affecting the shape of the loop, however,

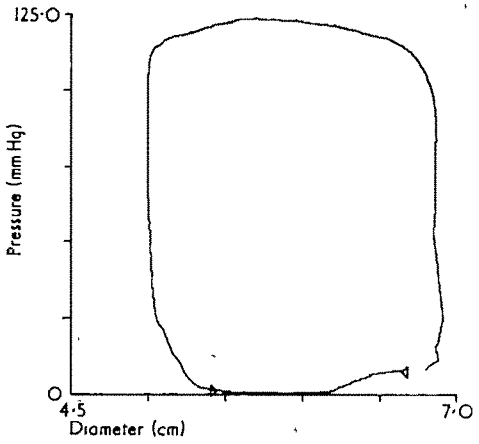

FIG. 7 *Pressure-dimension loop from a patient with severe mitral regurgitation but good left ventricular function (Case 20).*

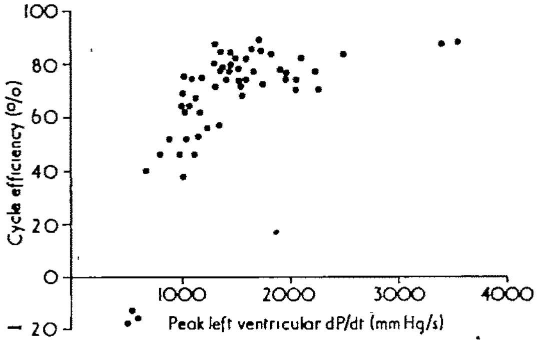

FIG. 9 *Relation between cycle efficiency and peak left ventricular dP/dt for all patients studied. Each point represents values from a single beat. Negative cycle efficiency indicates aneurysmal behaviour of the region giving rise to the echocardiographic dimension.*

was found to be the presence of left ventricular rather than valvular disease, and at least two processes could be identified. The first was a reduction in dimension as pressure rose, due either to asychronous onset of contraction (Rushmer, 1956a) or to an area behaving aneurysmally, suggesting the presence of a more compliant region elsewhere in the ventricle, and thus to a change in cavity shape during isovolumic contraction with corresponding absorption or dissipation of energy. The second abnormality was an increase in dimension, not attributable to ventricular filling when pressure was high at the end of systole, which might have been due to asynchronous termination of contraction, so that the region represented by the echo dimension was made to move passively by tension persisting elsewhere. It was this latter mechanism which led to the development of negative power components previously described, with corresponding reduction in efficiency. A number of processes might have been involved in the development of incoordinate contraction. These include abnormalities of activation, non-uniformity in the rate or extent of muscle shortening, distorted cavity shape, and inappropriate properties of connective tissue, with or without overt aneurysm formation. They all have in common an alteration in the phase relations between pressure and dimension changes stressing that the echo dimension reflects the behaviour of only a small part of the cavity.

The present results allow at least three independent types of disturbance to left ventricular systolic function to be defined. Depression of myocardial function associated with a reduction in the rate or force of left ventricular contraction is demonstrable, during ejection, by a corresponding drop in peak power. Structural abnormalities of the left ventricle reflected in a low ejection fraction may themselves interfere with function since an increase in left ventricular dimension is associated with a concomitant increase in wall tension at any given cavity pressure. Finally, incoordinate contraction, giving rise to reduced cycle efficiency also appears to be a cause of impairment of cardiac performance in patients with heart disease. These disturbances may occur singly or in combination. Even in the present small series, a number of different patterns were present: in Case 7, peak power, ejection fraction, and cycle efficiency were all reduced, while in Cases 17 and 26 cycle efficiency was normal, though both peak power and ejection fraction were reduced. Finally, in Cases 18 and 25, ejection fraction was normal and peak power reduced in both with cycle efficiency normal in one and reduced in the other. The results suggest, therefore, that impairment of left ventricular function in patients with heart disease is complex, and cannot be expressed by any single quantity. Rather, it seems that a number of independent mechanisms may be involved, and, using the present methods, information can be collected at routine cardiac catheterization which allows an initial analysis of the disturbance to be undertaken in individual patients.

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Assessment of left ventricular function by indices derived from aortic flow velocity

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The velocity and acceleration of aortic blood flow were measured by means of a catheter velocity probe in 40 patients during routine diagnostic cardiac catheterization. Ten different variables were derived from the aortic velocity measurements, and their ability to discriminate between good and bad left ventricular (LV) function was tested.

By means of eight conventional indices of LV function derived from pressure, mean flow, and quantitative cineangiography, the patients were divided into 3 groups: group 1, good LV function; group 2, moderate LV function; group 3, poor LV function.

Aortic peak velocity and maximal acceleration correlated well with stroke volume and were thus indices of LV pump function. Aortic peak velocity also showed a significant correlation with LV stroke work. Both aortic peak velocity and maximal acceleration failed to discriminate between the three groups of patients, and correlated poorly with conventional indices of LV function. The mean values of stroke volume differed significantly between groups 1 and 2, and between groups 1 and 3, and also correlated better with the conventional functional indices.

The best discrimination between normal and abnormal LV function was provided by dividing stroke volume by maximal acceleration, but stroke volume divided by peak velocity discriminated better than stroke volume alone. Stroke volume divided by maximal acceleration also gave more significant individual correlations with the conventional functional indices than did any other variable derived from aortic velocity.

The peak velocity and in particular the maximal acceleration of blood flow in the ascending aorta have been suggested as possible indices of left ventricular (LV) function (Rushmer, 1964; Noble, Trenchard, and Guz, 1966). Though catheter flow velocity probes capable of making the necessary measurements have been in existence for 10 years (Mills, 1966; Bond and Barefoot, 1967; Mills and Shillingford, 1967), there are few reports of their use in man to assess LV function (Bennett *et al.*, 1974; Jewitt *et al.*, 1974).

This paper presents our experience of aortic flow velocity measurements in 40 patients with a wide variety of cardiac disorders, and compares various possible indices of LV function derived from velocity measurements with more conventional functional indices derived from LV pressure and quantitative cineangiocardiography.

Subjects

The 40 patients, all undergoing routine diagnostic right and left heart catheterization, comprised 24 men and 16 women (mean age 50 years with a range of 26 to 68 years). In order to avoid errors of flow velocity measurement caused by jet effects and turbulent flow in the aorta, all patients with more than mild aortic stenosis or regurgitation were excluded.

Cardiac index (CI), left ventricular end-diastolic volume (LVEDV), ejection fraction (EF), normalized ejection rate (NER), peak mid-wall circumferential fibre shortening velocity (peak V_{CF}), left ventricular end-diastolic pressure (LVEDP), maximal velocity of contractile element shortening at zero load multiplied by the series elastic stiffness constant (KV_{max}), and KV_{max} after an ectopic beat with the resulting post-ectopic potentiation of contractility ($KV_{max}PE$), were used to divide the patients into three groups. Each of the above indices of LV function was scored 1 to 3, 1 representing a normal or near-normal value, 2 a moderately impaired value, and 3 a severely impaired value. The numerical values for each index determining its score are shown in Table 1. A final score for each left ventricle was obtained

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TABLE 1 *Values of indices of LV function used to assign patients to 3 functional groups*

Index	*Grade 1*	*Grade 2*	*Grade 3*
LVEDV ml/m^2	$<$100*	101–150	$>$150
LVEDP kPa (mm Hg)	$<$1·33 (10†)	1·46–2·66 (11–20)	$>$2·8 (21)
Cardiac index l/min per m^2	$>$2·0	1·2–1·99	$<$1·2
Ejection rate EDV/s	$>$2·0	1·5–1·99	$<$1·5
Peak V_{CF} circ/s	$>$1·5	1·0–1·4	$<$1·0
Ejection fraction	$>$0·50	0·30–0·49	$<$0·30
KV_{max}(s^{-1})	$>$70	55–69	$<$55
KV_{max}PE (s^{-1})	$>$150	100–149	$<$100

For explanation of abbreviations, see text.

*In cases with diastolic overload of the LV a LVEDV $\leqslant$110 ml/m^2 was allowed.

†In cases of restriction a LVEDP $<$2·66 kPa (20 mmHg) was allowed.

by averaging the scores of the individual indices. Thus, the normal case has a score of 1 for each of the 8 individual functional indices, and therefore a final average score of 1 (8/8). Patients were placed in group 1 if their final average score was 1·25 or less (allowing two individual functional index scores of 2, or one of 3, all the other scores being 1). Patients in group 2 had final average scores greater than 1·25 but less than 2·0, and group 3 patients all had average scores of over 2·0.

Group 1 (little or no impairment of LV function) contained 12 patients with mild organic disease (group 1a), and 6 patients with good LV function despite more serious cardiac lesions tending to limit the cardiac output (group 1b). Group 2 consisted of 13 patients with moderate impairment of LV function, and group 3 of 9 cases with poor LV function. The clinical and haemodynamic details of the patients are shown in Table 2, together with their average LV functional scores.

Methods

The exact nature of the investigation, including the measurement of aortic flow velocity, was explained to all the patients before the study, in order to obtain informed consent.

All patients were studied in the post-absorptive state after premedication with diazepam 10 mg and atropine 0·3 mg intramuscularly.

Cardiac output

This was measured from duplicate indocyanine-green dye dilution curves using a Gilford densitometer and the fore-'n-aft triangles method of calculation (Bradley and Barr, 1969) in 34 patients, and by the Fick method in the remaining 6 cases.

Left ventricular volumes

These were measured from LV cineangiograms taken in the right anterior oblique position at a frame speed of 48/s. The LV cavity and free wall thickness were outlined in successive frames covering a complete cardiac cycle using a light pen (Tektronix 4551) and computer (Varian 620 L/100). Volumes were calculated by the area-length method (Greene *et al.*, 1967), and the computer was programmed to display left ventricular end-diastolic volume (LVEDV), ejection fraction (EF), and normalized ejection rate (NER). The ejection rate was computed by linear regression analysis of the ejection phase of the LV volume/time relation, and normalized for LVEDV so that NER was expressed in EDV/s (Hood, Rackley, and Rolett, 1968). The computer also calculated midwall circumference (l) for each cineframe as $l=\pi(M+W)$, where M=minor axis and W=wall thickness. l plotted against time was differentiated to give midwall circumferential fibre velocity (V_{CF}). Peak V_{CF} was read directly from the computer plot of V_{CF} against time, and mean V_{CF} calculated by planimetric integration of the V_{CF}/time curve during the ejection phase of systole. Both peak and mean V_{CF} were normalized for end-diastolic midwall circumference and expressed in circumferences/s (Peterson *et al.*, 1973).

LV pressures

These were measured by Telco (MM52) or Millar micromanometers. Using the St. Thomas's Hospital long sheath technique (Brooksby *et al.*, 1974), these instruments were introduced into the LV either retrogradely across the aortic valve following Seldinger puncture of the right femoral artery, or antegradely across the mitral valve after transatrial septal puncture. The LV pressure and its first derivative (dp/dt) were recorded, and the LVEDP was measured at the start of the rapid rise in dp/dt with the onset of systole. Zero reference was taken as the sternal angle.

KV_{max} and KV_{max}PE

A special processor, triggered by the R wave of the electrocardiogram, continuously sampled the high fidelity LV pressure signal from the Telco or Millar micromanometer from R wave to onset of ventricular contraction (a point selected manually by the operator). At this point, the last sampled value of pressure was stored and subtracted from the pressure signal for the rest of the cardiac cycle to give LV developed pressure. The logarithm of LV developed pressure was differentiated to give dp/dt divided by developed pressure. This signal (representing velocity of contractile element shortening) appeared on the vertical axis of an X–Y oscilloscope, the LV pressure (representing force) appearing on the horizontal axis. The isovolumetric portion of the resulting 'force-velocity' loop was treated as a monoexponential curve and extrapolated to LVEDP (zero developed pressure) to obtain KV_{max} (Nejad *et al.*, 1971; Mirksy, Ellison, and Hugenholtz, 1971; Grossman *et al.*, 1971). The pressure processor containing a unity gain five-stage Thomson filter and differentiator had a frequency response flat to 50 Hz, and a constant time delay (8 ms) independent of frequency. It was also used to differentiate pressure signals to give dp/dt, or flow velocity signals to give acceleration.

As the calculation of KV_{max} may be incorrect if there

TABLE 2 *Clinical and haemodynamic data*

Case No.	*Sex*	*Age*	*Diagnosis*	*Heart rate*	*Cardiac index l/min per m²*	*Flow probe stroke volume ml*	*LV pressure*		*LV EDV ml/m²*	*Ejection rate EDV/s*	*Ejection fraction*	*Peak VCF circ/s*	*Mean VCF circ/s*	*dP/dt mm Hg/s*
							Systolic kPa (mm Hg)	*Diastolic kPa (mm Hg)*						
Group 1A														
1	M	60	IHD AS+AR 1/4	79 SR	3·26	64·0	24 (180)	1·07 (8)	85	2·25	0·55	1·1	0·57	2328
2	M	58	MS 1/4 MR trivial—AR 1/4	98 SR	2·14	46·2	16 (120)	0 (0)	41	4·3	0·51	—	—	2560
3	F	35	AS+AR 1/4	84 SR	2·6 F	91·0	16·6 (125)	1·07 (8)	82	1·42	0·76	3·1	0·91	1440
4	M	48	MS 1/4 AR 1/4	121 AF	1·97	32·0	16 (120)	0·53 (4)	36	3·4	0·64	1·66	0·6	2040
5	F	55	AR 2/4	70 SR	2·7 F	72·0	17·3 (130)	0·4 (3)	106	2·03	0·66	1·2	0·78	1200
6	M	34	IHD+MI	68 SR	2·92	63·3	15·3 (115)	0 (0)	92	7·36	0·83	3·5	1·92	2000
7	M	41	HOCM	68 SR	2·15	61·0	24 (180)	1·07 (8)	82	2·34	0·69	2·3	—	1800
8	F	50	MR 1/4 trivial MS+AR	49 SR	2·66	71	18·6 (140)	0·66 (5)	84	1·92	0·59	1·8	0·9	1800
9	M	38	IHD	66 SR	3·56	80·7	17·6 (132)	0·93 (7)	88	3·06	0·63	1·1	0·7	1760
10	M	39	IHD—MR 2/4 due to papillary muscle dysfunction	68 SR	2·36	60	16·6 (125)	1·07 (8)	75	3·18	0·47	1·38	—	1333
11	M	36	Neuromuscular chest pain	92 SR	3·2	43·1	16 (120)	0·67 (5)	62	2·91	0·47	1·3	0·78	1280
12	F	45	Essential hypertension, chest pain, MR 1/4	82 SR	3·03	66·9	29·3 (220)	0 (0)	61	6·46	0·93	3·9	1·85	2560
Group 1B														
13	F	65	MS 2–3/4 Minimal MR+AR	92 AF	1·20 F	47	16 (120)	0·27 (2)	90	2·73	0·65	2·29	1·3	1160
14	F	48	MS 2–3/4 minimal MR	79 SR	2·5	49	14·7 (110)	0·53 (4)	49	3·47	0·76	1·87	—	1700
15	F	51	Normally functioning MVP—TVP stenosed 2–3/4 and regurgitant 1/4	72 A.Fl.	3·2	59·5	16 (120)	0·93 (7)	87	3·13	0·69	1·5	1·2	1800
16	M	57	Restrictive cardiomyopathy+MR 2/4+TR 2/4	78 AF	3·0	44·5	18·66 (140)	2 (15)	104	2·53	0·65	1·7	0·7	2200
17	M	63	Constrictive pericarditis	80 AF	1·91 F	38	11·7 (88)	2·7 (20)	48·5	1·89	0·56	1·5	—	1058
18	F	60	Normally functioning MVP—TR 2–3/4	75 AF	3·3	65	14 (105)	0·27 (2)	85	3·03	0·60	1·5	—	1600
Mean values		48·4 9·5		78·9	2·69	58·8	17·7± 4·18	0·79± 0·69	75·4	3·19	0·646	1·92	1·0	1756
±ISD				15·4	0·52	15·0	(132·6± 31·3)	(5·9± 5·2)	20·9	1·53	0·12	0·84	0·46	463
Group 2														
19	M	52	CCM	102 A.Fl.	2·6	45·3	13·3 (100)	0·4 (3)	108	2·12	0·50	1·48	0·64	1160
20	F	57	IHD—MI+LV aneurysm	96 SR	1·9 F	23·0	14·7 (110)	3·3 (25)	87	—	0·16	—	—	1000
21	M	54	MS 2/4—minimal MR; AS+AR 1/4; rheu. myoc. involv.	77 AF	1·8	71·8	18·7 (140)	1·33 (10)	79	2·6	0·63	—	—	1860
22	M	52	MR 3/4	80 AF	2·1	40·3	14·7 (110)	2·4 (18)	143	1·68	0·59	1·27	0·54	1440
23	F	50	MR 2–3/4 MS 1–2/4	80 AF	2·71	62	17·3 (130)	0·27 (2)	175	2·82	0·49	1·4	0·5	1760

KV_m s^{-1}	KV_{max} PE s^{-1}	*Mean velocity cm/s*	*Peak velocity cm/s*	*Maximal acceleration cm/s²*	*Stroke work joules g×m*	*LVPP Watts g×m/s*	*Average LV functional score*
118	294	8·5	64·1	1040	—	10·63 (1083·8)	1 125
100	180	8·1	28·3	773	0 616 (62·8)	4 22 (430·45)	1·0
75	112	8 1	46·8	940	1·073 (109·4)	11·61 (1184)	1·250
120	242	6·6	29·0	552	—	4·39 (448·2)	1·125
156	265	12·0	55·5	831	1·147 (117)	6·64 (677·7)	1·125
98	188	10·8	40·4	744	0·709 (72·3)	4 11 (419·6)	1·0
110	150	7·3	32·0	713	—	6 95 (708·9)	1·0
100	125	6·9	47·5	921	1·255 (128)	5·45 (556·4)	1·125
134	158	14 7	62·6	1030	1·129 (115·2)	6·26 (638·8)	1 125
110	145	9·9	41·8	700	0·882 (90·0)	4 28 (436·4)	1·125
110	150	13·5	52·6	891	—	4 52 (460·7)	1·250
240	450	14·4	55·0	700	1·765 (180)	10 0 (1020·3)	1·0
93	175	9·0	41·1	630	0·593 (60 5)	5·22 (532)	1 0
155	—	6·8	27·8	860	—	3·77 (385)	1·0
92	152	9·6	45·5	722	—	5·14 (524·4)	1·0
150	250	9·8	33·5	627	—	3·49 (356)	1·125
195	197	6·4	20·6	450	—	1·49 (152·4)	1·250
180	190	14·9	57·3	1054	—	4 29 (438·2)	1 0
135·3 ± 50·9	201 3 ± 81·6	9·85 ±2·9	43·5 ±12·8	788 ±171	—	5·69± 2·64 (580 5± 270)	
62	110	8·93	31·8	860	—	3·55 (362)	1·5
120	160	4·1	18·2	534	0·186 (19)	1·87 (190 8)	1 83
78	100	6·6	37·6	1456	0·729 (74 4)	9·18 (936·8)	1·285
67	88	6·8	49	914	0·608 (62·0)	4 74 (483·7)	1·875
76	136	11·8	57·5	861	0 971 (99)	6 87 (700 6)	1·625

are major abnormalities of segmental wall motion (Sonnenblick *et al.*, 1970), KV_{max} and KV_{max}PE were not used in the correlations in 5 patients with ischaemic heart disease who had obvious LV dyskinesia on cine-angiography. As there is evidence that mitral regurgitation does not invalidate the calculation of KV_{max} from pressure, presumably because the largest values of contractile element velocity occur early in systole when the inertia of the blood in the ventricle has delayed a significant volume change (Falsetti *et al.*, 1971), patients with mitral regurgitation were included in this part of the study.

Aortic flow velocity

This was measured in the ascending aorta 4 to 5 cm above the aortic valve using a Carolina Medical Electronics intravascular flow velocity probe (7 FG), and the CME Model 601D 'Cliniflow' square-wave electromagnetic flowmeter. This instrument is completely patient isolated, extremely simple to use, and can be provided with factory-calibrated probes if so desired. It has a frequency response that is −2dB at 10 Hz, and −18dB at 30 Hz. The phase shift is linearly related to frequency with a time delay of 37 ms ±3 ms in the frequency range 1 Hz to 30 Hz. Because of the electrical environment in our laboratory, the velocity signal from the flowmeter was still unacceptably 'noisy', and was, therefore, passed through a 12 Hz low-pass filter (frequency response −2 dB at 10 Hz, and −18 dB at 30 Hz, with a constant time delay of 25 ms).

By passing a cosine squared pulse from a signal generator through this filter and recording the original signal and the filtered wave form for different values of base-width, together with their first derivatives, it was possible to show that 'peak velocity' was attenuated by 0, 1·5, 6·1, and 10·6 per cent, at base widths of 500, 240, 120, and 100 ms, respectively. The corresponding attenuations of 'maximal acceleration' were 0, 2, 14, and 25·7 per cent. With the flowmeter and filter in series (both having the same frequency response), the attenuation of peak velocity and maximal acceleration are just under twice the values obtained with the filter alone. The base-widths below which the percentage attenuation exceeds 5 are 190 ms for peak velocity and 230 ms for maximal acceleration. Base-widths of under 230 ms were in fact observed in 8 of the 40 patients studied (Cases 20, 26, 31, 32, 33, 34, 35, 38), under 190 ms in only 1 patient (Case 33). In the patient with the smallest base-width (175 ms) peak velocity was attenuated by 6·1 per cent and maximal acceleration by 12 2 per cent. These results are in keeping with Gabe's work on pressure waveforms using a similar filter (Gabe, 1972).

The catheter velocity probe was passed to the ascending aorta through a long sheath after Seldinger puncture of the femoral artery. Previous workers (Gabe *et al.*, 1969; Bennett *et al.*, 1974) were unable in some patients to pass the flow probe to ascending aorta from brachial artery. In no case in the present series did it prove impossible to position the probe in ascending aorta. Particular care was taken to avoid angulation and undue movement of the probe, and the position and stability of the velocity sensor were verified from cineradiographs.

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TABLE 2 *(continued)*

							LV pressure							
Case No.	*Sex*	*Age*	*Diagnosis*	*Heart rate*	*Cardiac index l/min per m²*	*Flow probe stroke volume ml*	*Systolic kPa (mm Hg)*	*Diastolic kPa (mm Hg)*	*LV EDV ml/m²*	*Ejection rate EDV/s*	*Ejection fraction*	*Peak VCF circ/s*	*Mean VCF circ/s*	*dP/dt mm Hg/s*
24	M	54	CCM; complete AV block	62 paced	2·07	33·3	13·3 (100)	0·53 (4)	106	1·02	0·36	1·44	—	540
25	F	62	MS 2–3/4 MR 1/4	94 AF	2·4	33·0	16 (120)	1·33 (10)	74	1·78	0·32	1·25	—	1360
26	F	58	Angina with normal coronary arteries	105 SR	2 8	24·5	17·3 (130)	0·66 (5)	93	2·33	0·60	1·0	—	2000
27	M	43	IHD—MI	99 SR	5 0	70·7	16 (120)	2·66 (20)	138	1·91	0·44	0·9	—	2200
28	M	57	MS 1/4 rheumatic myocardial involv.	60 AF	1·76	49·0	16·3 (122)	0·66 (5)	89	2·87	0·60	1·0	—	1100
29	F	46	MR 2–3/4 MS 1–2/4	100 SR	3·9	47·5	21·3 (160)	2·93 (22)	102	2·05	0·53	1·45	0·74	1920
30	M	57	IHD+MI	75 SR	2·6	56	17·3 (130)	0·66 (5)	169	1·53	0·36	0·8	—	1560
31	M	26	Early CCM	120 SR	2·2 F	20·6	16 (120)	0 (0)	74	2·78	0·55	1 1	0·62	2200
Mean values ±ISD		51·4 9·2		88·4± 17·6	2·6± 0·91	44·3± 17·4	16·3± 2·2 (121·5± 16·7)	1·32± 1·12 (9·9± 8·4)	110·5 ± 34·7	2·12± 0·58	0 47± 0 141	1·19 ± 0·24	0·61 ± 0·09	1546 ± 504
Group 3														
32	M	54	CCM	91 SR	2·5	28	14·4 (108)	2·27 (17)	257	0 6	0·18	0·6	0·16	720
33	F	65	Essential hypertension	93 AF	1·8	17	20 (150)	2 4 (18)	100	2·03	0 52	0·78	0·39	1280
34	M	52	MR 2/4 AR 1–2/4 past history of SBE	101 SR	1·6	16	10·7 (80)	2·53 (19)	84	1·62	0·25	0·9	0·42	1000
35	M	55	Normally functioning MVP; ASD (? dilated foramen ovale) PH of SBE	98 AF	1·7	20 7	12·6 (95)	1·07 (8)	280	0·48	0·22	—	—	760
36	M	32	IHD+MI	85 SR	3·5	57·5	14·6 (110)	3·33 (25)	136	1·38	0·41	1·1	0·69	1220
37	M	67	IHD+MI	83 SR	2·2	39·9	16 (120)	3·33 (25)	240	0·41	0·11	1·0	—	1920
38	F	57	CCM	92 SR	2·2	35 4	13 3 (100)	2·4 (18)	118	0·57	0·12	0·43	—	700
39	F	32	MS 3/4; minimal MR; rh myocardial involvement	88 AF	1·7	31·4	21·3 (160)	0·933 (7)	101	1·43	0·34	0 6	0·28	1316
40	M	47	IHD+MI+LV aneurysm	88 SR	3·1	38·4	18·6 (140)	3·33 (25)	183	1·77	0·32	0·8	—	2000
Mean values ±ISD		51·2 12·5		91·0 5·8	2·25 0·67	31·6 13·2	15·7± 3·6 (118·1± 26·8)	2·39± 0·9 (18± 6·8)	166·5 ± 75·4	1·14± 0·63	0·274± 0·136	0·77 ± 0·22	0·39 ± 0·19	1213 ± 486
Statistical significance of difference of mean values														
Group 1 v. 2		NS		NS	NS	P 0·025	NS	NS	P 0·005	P 0·05	P 0·005	P 0·01	NS	NS
Group 2 v. 3		NS		NS	NS	NS	NS	P 0·05	P 0 05	P 0·005	P 0·005	P 0·005	NS	NS
Group 1 & 3		NS		P 0 05	NS	P 0·001	NS	P 0·001	P 0·001	P 0·001	P 0·001	P 0·001	P 0·01	P 0·01

Footnote: AF—Atrial fibrillation; A.Fl.—atrial flutter; AR—aortic regurgitation; AS—aortic stenosis; ASD—atrial septal defect; CCM—congestive cardiomyopathy; HOCM—hypertrophic obstructive cardiomyopathy; IHD—ischaemic heart disease; MI—myocardial infarction; MR—mitral regurgitation; MS—mitral stenosis; MVP—mitral valve prosthesis; SBE—subacute bacterial endocarditis; SR—sinus rhythm; TR—tricuspid regurgitation; TVP—tricuspid valve prosthesis. F denotes Fick estimation

KV$_{max}$ s^{-1}	*KV*$_{max}$ *PE* s^{-1}	*Mean velocity cm/s*	*Peak velocity cm/s*	*Maximal acceleration cm/s²*	*Stroke work joules g×m*	*LVPP Watts g×m/s*	*Average LV functional score*
61	103	3·5	20·4	443	—	2·56 (261)	1·875
73	94	6·4	25·2	608	0·490 (50)	3·0 (306·3)	1·625
64	142	6·6	20	402	0·441 (45)	2·13 (216·9)	1·375
90	285	16·4	52	939	—	4·96 (505·6)	1·750
60	75	7·0	33·0	673	0·725 (74)	3·54 (361)	1·625
110	170	14	57·4	930	—	5·96 (608·6)	1·375
60	150	11·1	54·9	902	—	5·87 (599·0)	1·875
52	72	6·9	29·3	455	—	2·81 (286·9)	1·625
74·8 ± 20·4	129·6 ± 56·7	8·47 ± 3·8	37·4 ± 14·9	767 ± 291	—	4·39 ± 2·14 (447·6 ± 218·2)	
43	44	5·6	26·4	600	0·343 (35)	2·44 (248·9)	2·625
41	72	2·9	17·7	392	—	2·83 (288·5)	2·0
60	90	4·4	20·4	370	—	1 05 (106·9)	2·25
52	72	3·7	25·2	538	—	2·38 (242·8)	2·57
60	88	11·2	45·5	959	—	3·74 (381·2)	2·25
85	182	5·8	32·4	530	—	3·92 (399·4)	2·125
60	135	8·8	51·0	701	0·304 (31)	3·43 (350)	2·250
50	120	9·5	38·1	728	—	3·75 (382·9)	2·125
130	155	8·4	43·2	864	—	4·46 (454·9)	2·0
64·5 ± 27·7	106·4 ± 44·6	6·7 ± 2·8	33·3 ± 11·8	631 ± 200	— —	3·11 ± 1·04 (317·3 ± 106·3)	
P 0·001	P 0·02	NS	NS	NS	—	NS	
NS P 0·001	NS P 0 005	NS P 0·02	NS NS	NS P 0·05	— —	NS P 0·01	

Stabilization of the probe was facilitated by its tapering tip extending 6 cm beyond the velocity sensor (Jewitt *et al.*, 1974).

The same probe was used in all patients, and was calibrated in normal saline (NaCl 0·15 mol/l) using a special flow rig. The probe was inserted through a watertight sleeve into a glass tube of internal diameter 1·42 cm. An electric pump circulated the saline from a reservoir through a rotameter, and then via the glass tube containing the probe back to the reservoir. The volume of flow could be adjusted by a tap downstream to the rotameter, the accuracy of which was confirmed by timed volume collections. After establishing a true zero reading, flow was adjusted to give velocities of 10, 20, and 40cm/s in the glass tube, and the 'probe factor' control on the flowmeter adjusted until the appropriate mean velocity appeared on the digital meter. Flow was then reversed in the tube and the process repeated. Over this range of velocities, and with this probe, the 'probe factor' control setting varied by not more than 8 per cent. Before each insertion of the probe into a patient, it was zeroed in a bowl of sterile saline, and the zero obtained in this way did not differ from the assumed zero velocity occurring late in diastole (Hoffman *et al.*, 1965).

Using this zero, ***peak velocity*** (PV) was measured directly from the velocity record in 10 consecutive beats. The velocity signal was also differentiated to give acceleration, and ***maximal acceleration*** (MA) measured for the same 10 beats. ***Mean velocity*** (MV) was derived by planimetric integration of the area under the velocity curve for the 10 beats. The ***flow probe cardiac output*** was obtained by multiplying MV by 60 × aortic cross-sectional area. The aortic diameter was measured from aortograms, and cross-sectional area obtained after correction for magnification from πr^2. The ***flow probe stroke volume*** (SV) was the cardiac output/heart rate. ***Peak aortic flow*** (ml/s) was given by aortic peak velocity (PV) × aortic cross-sectional area. LV peak power (LVPP) was calculated from the formula:

$$\text{LVPP (g m/s)} = \frac{\text{Peak aortic flow} \times \text{peak LV developed pressure (mm Hg)} \times 1{\cdot}36}{100}$$

in SI units:

$$\text{LVPP (watts)} = \text{Peak aortic flow (ml/s)} \times \text{peak LV dev. press. (kPa)} \times 10^{-3}$$

This value for LVPP is a close approximation, since peak aortic flow occurs just before peak LV or aortic pressure. Fig. 1 shows simultaneous aortic flow and pressure, and Fig. 4 simultaneous aortic flow and LV pressure. The flow signal has a total transit time of 62 ms (37 ms for the flowmeter, and 25 ms for the filter), and if allowance is made for this then peak flow precedes peak LV or aortic pressure by 20 to 90 ms.

In 18 patients in whom simultaneous LV and aortic pressures were recorded, LV stroke work (LVSW) was calculated:

$$\text{LVSW (g m)} = \frac{\text{Flow probe SV} \times (\overline{\text{LVSP}}\text{–LVEDP mm Hg}) \times 1{\cdot}36}{100}$$

In SI units:
LVSW (joules) =

$$SV\,(ml) \times (\overline{LVSP} - LVEDP\ kPa) \times 10^{-3}$$

Where $\overline{LVSP}$ is the mean LV pressure during ejection obtained by planimetric integration of the area of the LV pressure curve contained between the beginning of the upstroke and the incisura of the aortic pressure curve (Covell *et al.*, 1966).

All pressure and flow signals were recorded on a Philips 'Analog-Seven' tape recorder together with the electrocardiogram. Selected periods of tape-recorded data were replayed onto a Cambridge twelve channel photographic recorder.

The mean values of the various indices of LV function obtained in each of the three groups of patients were compared using Student's t test for unpaired data. Correlations between different indices of function were carried out by least squares regression analysis. The statistical significance of the correlation coefficient (r value) was tested by the formula:

$$t = \sqrt{\frac{r^2 \times (N-2)}{1-r^2}} \quad \text{(Croxton, 1953).}$$

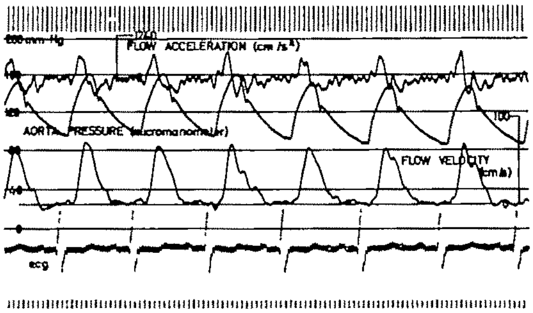

FIG. 1 *Aortic flow velocity (third tracing from top) recorded simultaneously with aortic pressure (Millar micromanometer—second tracing from top). Flow acceleration (top) and electrocardiogram (bottom) also shown. Flow velocity tracing delayed by 62 ms so peak velocity precedes peak aortic pressure by some 80 ms.*

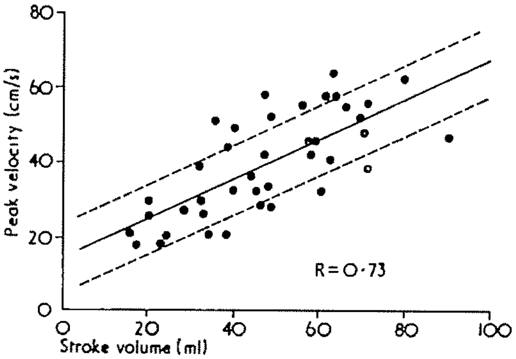

FIG. 2 *Peak velocity plotted against flow probe stroke volume in 40 patients. R=0·73, P<0·001, Y=0·23X+22·27.*

Results

The clinical and haemodynamic data of the 40 cases studied are shown in Table 2. Aortic peak velocity (PV) and aortic maximal acceleration (MA) showed an excellent linear correlation ($r=0{\cdot}71$; $P<0{\cdot}001$). There was also good correlation between PV and stroke volume (SV) ($r=0{\cdot}73$; $P<0{\cdot}001$—Fig. 2), and between MA and SV ($r=0{\cdot}755$; $P<0{\cdot}001$—Fig. 3). This dependence of PV and MA on SV is further illustrated in Fig. 4. Fig. 4 shows aortic flow velocity, LV pressure, and dP/dt in a patient with congestive cardiomyopathy and complete heart block. PV and MA in this patient were low, averaging 20·4 cm/s and 443 cm/s², respectively. It can be seen, however, that whenever the PR interval fell between 100 and 280 ms, PV was obviously higher with a concomitant increase in LV peak pressure and max. dP/dt. Thus, the increase in SV resulting from a well-timed atrial contraction was reflected by an increase in PV. In 2 patients, LV pressure alternans developed during pacing. Alternation of both PV and MA accompanied the alternation of SV and LV peak pressure. PV also correlated well with LVSW ($r=0{\cdot}70$; $P<0{\cdot}005$) in the 18 patients in whom it was possible to calculate LVSW. That this was not entirely because of the good correlation between PV and SV is suggested by the fact that there was a small but significant positive correlation in all 40 cases between PV and LV peak developed

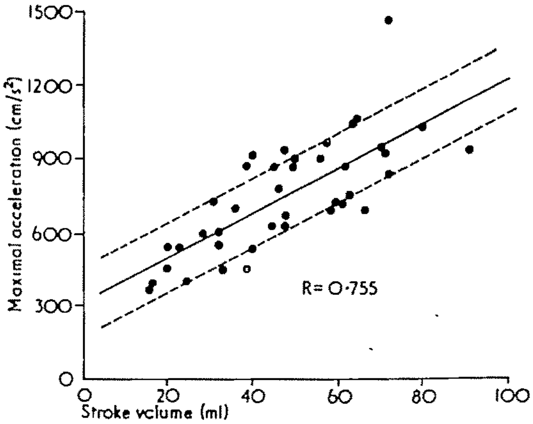

FIG. 3 *Maximal acceleration plotted against flow probe stroke volume in 40 patients. R=0·755, P<0·001, Y=9·15X+306·8.*

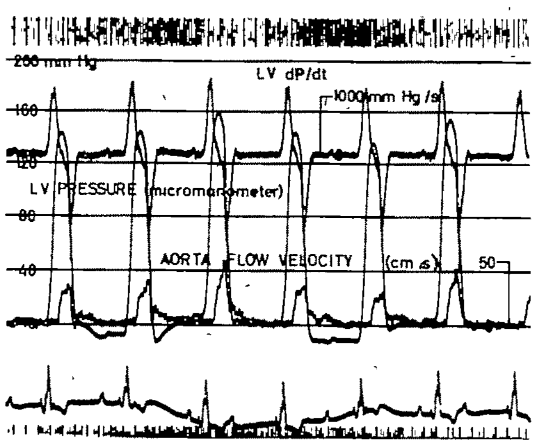

FIG. 4 *LV dP/dt, pressure, aortic flow velocity, and electrocardiogram in a patient with heart block and congestive cardiomyopathy. Note increase in LV peak pressure and max dP/dt associated with the rise in peak velocity when PR interval falls between 100 and 280 ms. RV pacing at a rate of 62/min.*

pressure ($r=0·383$; $P<0·02$). Fig. 5a shows SV, Fig. 5b PV, and Fig. 5c MA values obtained in patients considered to have normal or near-normal LV function (group 1), moderate impairment of function (group 2), and severe impairment of function (group 3).

The mean values of SV obtained in the three groups (group 1: 58·8±15.0 ml—mean±SD; group 2: 44·3±17·4 ml; group 3: 31·6±13·2 ml) show a barely significant difference ($P<0·025$) between groups 1 and 2, no significant difference between groups 2 and 3, and a highly significant difference ($P<0·001$) between groups 1 and 3. The mean values of PV (group 1: 43·5±12·8 cm/s; group 2: 37·4±14·9 cm/s; group 3: 33·3±11·8 cm/s) do not differ significantly. The differences of the mean values of MA (group 1: 788±171 cm/s^2; group 2: 767±291 cm/s^2; group 3: 631±200 cm/s^2) just reach statistical significance ($P<0·05$) between groups 1 and 3 only.

In order to see if these results were influenced by the inclusion in group 1 of 6 patients with significant organic heart disease but relatively unimpaired LV function (group 1b), these patients were excluded and the results recalculated. The mean SV for group Ia was 62·4±16·3 ml, mean PV 46·3±12·3 cm/s, and mean MA 820±148 cm/s^2. The differences in SV became more significant ($P<0·01$) between groups 1a and 2, and remained highly significant ($P<0·001$) between groups 1a and 3.

The differences in the mean PV just reached statistical significance ($P<0·05$) between groups 1a and 3, and those for MA did not change. Fig. 5a, 5b, and 5c show the large overlap in values of SV, PV, and MA between the three groups of patients, and suggests that in the individual case PV and MA (and to a lesser extent SV) are insensitive indices of LV function.

In an attempt to correct for the dependency of PV and MA on SV, the SV was divided by either PV or MA. Fig. 5d shows the values of SV/MA, and Fig. 5c those for SV/PV in the three groups of patients studied. In particular, SV/MA distinguished well between patients with good and bad LV function, the difference of the mean values of this 'flow fraction' being highly significant between groups 1 and 2 ($P<0·005$), and between groups 1 and 3 ($P<0·001$). The fraction SV/PV was less sensitive, since the difference between groups 1 and 2 did not reach statistical significance, though the difference between groups 1 and 3 was again highly significant ($P<0·001$). The use of these fractions clearly allowed a much better separation of the patients in the three functional groups than did either PV or MA alone. SV/MA also proved superior to SV alone in discriminating between patients with good and bad LV function.

Fig. 6 and 7 show the distribution of the other indices of LV performance between the three groups of patients. Using any single index of function, there is some overlap between individual patients in the three groups, despite the fact that each index (except max. dP/dt and mean V_{CF}) shown in these figures was used to determine the functional group to which the patient was assigned. The best single discriminatory index in this array of tests of LV function was the ejection fraction.

In order to evaluate further the ability of the velocity measurements to assess LV performance, each of them was separately correlated against seven indices of LV function derived from LV pressure or LV volume measurements using least squares regression analysis. Table 3 gives the results of this analysis, the number of patients, the r value, and the P value for each correlation. Mean velocity (MV) just correlated significantly with mean V_{CF}, max dP/dt, and ejection fraction, but a more significant correlation was obtained with KV_{max}, and in particular with $KV_{max}PE$.

PV showed a barely significant correlation with max dP/dt, and a slightly better correlation with $KV_{max}PE$. The other correlations were not significant.

MA showed no significant correlation with any of the other indices of LV function tested.

Flow probe stroke volume (SV) correlated signi-

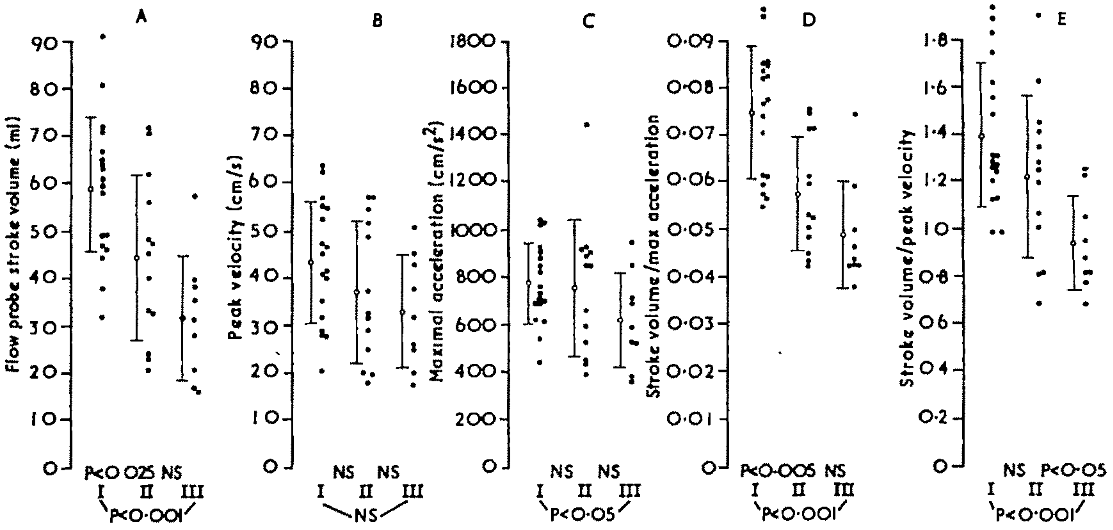

FIG. 5 *Values of flow probe stroke volume, peak velocity, maximal acceleration, stroke volume/maximal acceleration, and stroke volume/peak velocity obtained in 40 patients divided into 3 groups. Group 1: patients with near-normal LV function. Group 2: moderate impairment of LV function. Group 3: poor LV function. Also shown are mean ± SD for each variable and each group. NS=not significant. P values indicated at bottom.*

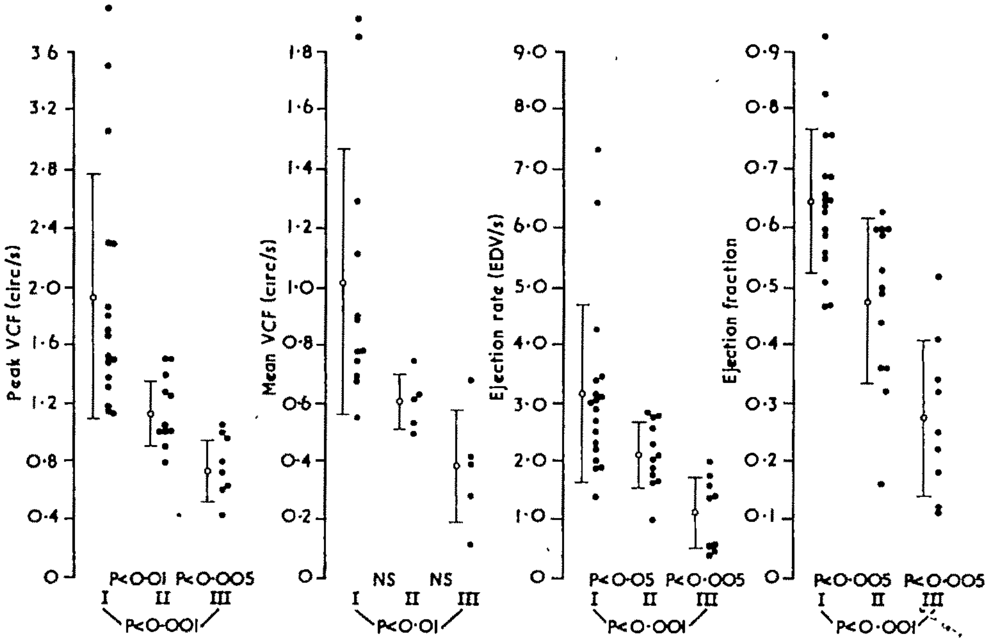

FIG. 6 *Values of peak V_{CF}, mean V_{CF}, normalized ejection rate, and ejection fraction obtained by quantitative LV cineangiography in 40 patients divided into 3 functional groups. Also shown are mean ± SD for each variable and each group. NS=not significant. P values indicated at bottom.*

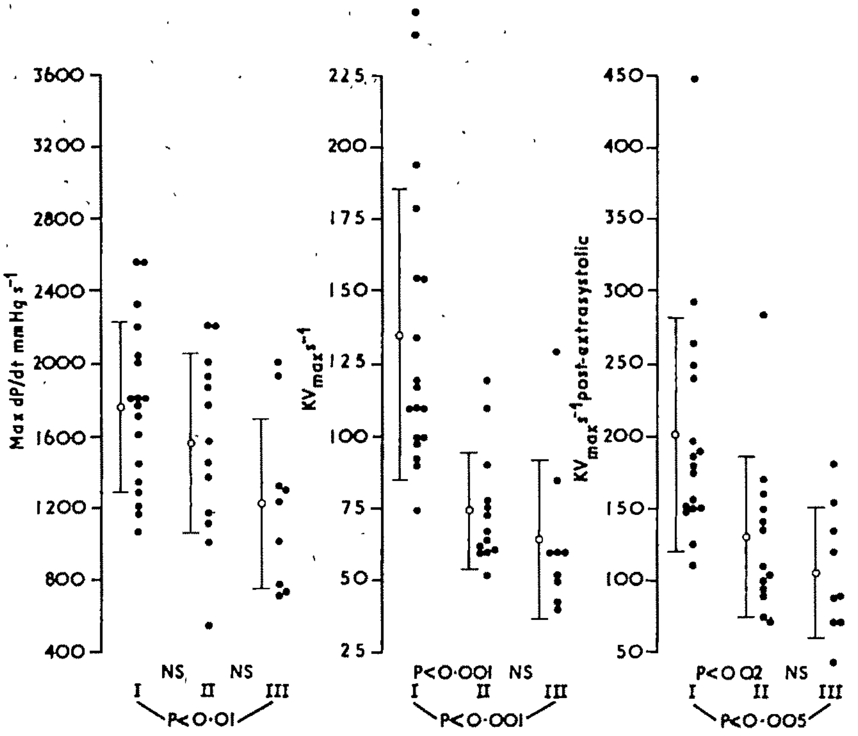

FIG. 7 *Values of Max dP/dt, KV_{max}, and $KV_{max}PE$ obtained from LV micromanometer pressure records in 40 patients divided into 3 functional groups. Also shown are mean ± SD for each variable and each group. NS = not significant. P values indicated at bottom.*

TABLE 3 *Correlation coefficients between indices of LV function derived from flow velocity and those derived from pressure and quantitative cineangiography*

Variable	*Mean VCF circ/s N=22*	*Peak VCF circ/s N=36*	*Ejection rate EDV/s N=39*	*Ejection fraction N=40*	*Max dP/dt N=40*	*KV_{max} N=35*	*$KV_{max}PE$ N=34*
Flow probe stroke volume	R=0 484 P <0·025	R=0·47 P <0·005	R=0 33 P <0·05	R=0·556 P <0·001*	R=0·376 P <0·02	R=0·389 P <0 025	R=0·387 P <0·025
Peak velocity	R=0·272 NS	R=0·122 NS	R=0·168 NS	R=0·272 NS	R=0·318 P= <0 05	R=0 307 NS	R=0·439 P <0·02
Maximal acceleration	R=0 08 NS	R=0·1 NS	R=0·117 NS	R=0 279 NS	R=0·289 NS	R=0 14 NS	R=0·114 NS
Mean velocity	R=0 43 P <0·05	R=0·2 NS	R=0·3 NS	R=0·34 P <0 05	R=0·393 P <0·01	R=0·491 P <0·005	R=0·527 P <0·005
Peak power	R=0·291 NS	R=0·449 P <0·01	R=0·222 NS	R=0·476 P <0·005	R=0·475 P <0·005	R=0·253 NS	R=0·495 P <0·005
Mean velocity/max. acceleration	R=0·558 P <0·01	R=0·235 NS	R=0·424 P <0·01	R=0·293 NS	R=0 290 NS	R=0·498 P <0 005	R=0·570 P <0 001
Peak velocity/max. acceleration	R=0 475 P <0 025	R=0·154 NS	R=0·135 NS	R=0·136 NS	R=0·25 NS	R=0·261 NS	R=0·517 P <0·005
Stroke volume/max. acceleration	R=0·719 P <0·001*	R=0 651 P <0·001*	R=0·396 P <0·02	R=0·565 P <0·001*	R=0 243 NS	R=0·514 P <0 005	R=0·517 P <0·005
Stroke volume/peak velocity	R=0·473 P <0 05	R=0·522 P <0·005	R=0 262 NS	R=0·453 P <0·005	R=0 01 NS	R=0 252 NS	R=0·10 NS
Peak power/max. acceleration	R=0 418 NS	R=0·552 P <0·001*	R=0·269 NS	R=0·484 P <0·005	R=0 454 P<0·005	R=0·296 NS	R=0·624 P <0 001*

*Highly significant correlation.

ficantly with mean V_{CF}, peak V_{CF}, NER, ejection fraction, KV_{max}, and $KV_{max}PE$; the best correlation being with ejection fraction.

Peak power (LVPP) correlated significantly with peak V_{CF}, ejection fraction, max dP/dt and $KV_{max}PE$.

MV/MA just correlated significantly with mean V_{CF}, NER, and somewhat better with KV_{max} and $KV_{max}PE$.

PV/MA proved disappointing, correlating only with mean V_{CF} and $KV_{max}PE$.

The 'flow fractions' SV/MA, and SV/PV did considerably better. In particular, SV/MA correlated well with all other indices of LV function except max dP/dt (Table 3) LVPP/MA correlated well with peak V_{CF}, EF, max dP/dt and $KV_{max}PE$.

Discussion

Despite much progress in the past 15 years, the search for better methods of assessing left ventricular function continues. In intact man, the performance of the left ventricular pump depends not merely on the state of the myocardium and the efficiency of the heart valves, but also on sympathetic nervous impulses, circulating catecholamines, the filling pressure of the pump (preload), and the load against which it has to eject (afterload). It is not surprising, therefore, that measurements of pressure and mean flow (cardiac output, stroke volume, stroke work, etc.), though useful in detecting directional changes in the same patients, are of limited value in comparisons between patients (Braunwald and Ross, 1964; Braunwald *et al.*, 1969). The rate of rise of LV pressure (dP/dt) also has limitations in the evaluation of myocardial contractility in man (Mason, 1969).

With the application of Hill's work on skeletal muscle (Hill, 1938) to isolated heart muscle (Abbott and Mommaerts, 1959; Sonnenblick, 1962; Brady, 1965), and subsequently to the intact human heart (Hugenholtz *et al.*, 1970; Mason, Spann, and Zelis, 1970; Falsetti *et al.*, 1971), it was hoped that V_{max}—the velocity of contractile element shortening at zero load—would provide a valid measure of LV contractility. The determination of V_{max} in the intact human heart is, however, based on a number of assumptions that are open to question, and also presents certain practical difficulties (Mirsky *et al.*, 1971, 1974). Its independence of preload has also been challenged (Noble, Bowen, and Hefner, 1969; Pollack, 1970; Nejad *et al.*, 1971). The use of quantitative angiocardiography to assess LV function is based on assumptions about ventricular geometry that may not be valid, especially in the presence of LV dyskinesia. The contrast medium temporarily depresses the function being measured so that continuous or even repetitive measurements are not possible. LV volume measurements are, moreover, extremely time consuming.

Experimental studies in dogs led Rushmer (1964) to suggest that MA was a sensitive index of LV performance. MA, PV, and SV have all been shown to reflect changes in LV contraction induced by positive inotropic stimulation (Noble *et al.*, 1966; Ross *et al.*, 1966) or by coronary artery ligation (Noble *et al.*, 1966) and experimental heart failure (Ross, Covell, and Sonnenblick, 1967)

Normal values for PV and MA in man have not yet been established. PV values averaging 56·3 cm/s (Rudewald, 1962), ranging from 54–80 cm/s (Gabe *et al.*, 1969) and of 67 and 83 cm/s (Bennett *et al.*, 1974) have been reported in patients with apparently normal LV function. MA values averaging 1969 cm/s^2 (Rudewald, 1962) and of 1894, 1556, and 1510 cm/s^2 (Bennett *et al.*, 1974) were obtained in the same patients; Gabe and co-workers (1969) did not measure MA.

The values for PV and MA obtained in our group 1 patients were lower than those quoted above. Electrical isolation from the patient in the CME 601D flowmeter has been achieved at the cost of some reduction in frequency response compared to their other models and to the instruments used by earlier workers (Gabe *et al.*, 1969; Bennett *et al.*, 1974; Jewitt *et al.*, 1974). This is, we believe, a small price to pay for the increase in safety and ease of use of this flowmeter. As stated in the methods section, PV attenuation exceeding 5 per cent occurred in one patient only (6·1% attenuation), and MA attenuation over 5 per cent in 8 patients (the worst attenuation was 12·2%). It seems unlikely, therefore, that the lower values for PV and MA obtained in our group 1 patients compared with the 'normal subjects' of other workers is because of the frequency response of the CME 601D flowmeter. Only 1 of the 18 patients in group 1 had no demonstrable heart disease, and the relatively low CI and SV values obtained in many of them may have been in part because of diuretic therapy before study. Routine premedication with atropine also resulted in some increase in resting heart rate with a concomitant decrease in SV.

Both PV and MA proved to be highly dependent on SV (Fig. 2 and 3), and this was well illustrated in the patients with complete heart block (Fig. 4) and pulsus alternans. Benchimol *et al.* (1969), using a Doppler flow probe, have reported similar findings, and have also shown that PV correlates well with the length of the preceding RR interval in patients in atrial fibrillation, an observation since confirmed by Jewitt *et al.* (1974).

To determine SV continuously using the intravascular velocity probe requires a measurement of aortic cross-sectional area which, in intact man, can only be made either by aortography or by echocardiography. The good correlation between velocity probe SV and both PV and MA in the present study means that these two simple velocity measurements satisfactorily reflect the performance of the LV pump, and can be used to follow the course of the critically ill patient without the need to measure aortic cross-sectional area in order to calculate SV. PV and MA have indeed been shown to be superior to aortic pressure in assessing the progress of patients in the intensive care unit (Jewitt *et al.*, 1974; Cross and Light, 1974).

PV and MA in the individual patient are, however, determined by the complex relation between the velocity and extent of shortening of each myocardial fibre, the size and geometry of the LV, and the cross-sectional area of the aorta. Thus, the failure of PV and MA to separate the three functional groups of patients in the present study is not altogether surprising. The dependence of these two variables on SV (itself greatly influenced by changes in preload and heart rate) limits their value in comparisons between patients. Noble *et al.* (1966) reported that MA in dogs was independent of postural changes, and, therefore, suggested that it was independent of preload. The good correlation between MA and SV in the present study makes this very unlikely. Van den Bos *et al.* (1973) have suggested that changes in MA are also inversely related to changes in afterload, and such a relation has indeed been demonstrated for PV and after-load (Ross *et al.*, 1966).

The poor correlations between PV and MA and the other indices of LV function in the present study contrast with the report of Bennett *et al.* (1974) that both PV and MA correlated well with ejection fraction, and clearly separated their 3 normal subjects from the 9 cases with coronary artery disease. Their data show that in their relatively few patients, deterioration of LV function was accompanied by an increase in heart rate and a decrease in cardiac index. Stroke index calculated from their data was thus progressively reduced as ejection fraction fell, and correlated well with MA (r=0·729), with PV (r=0·744), and with ejection fraction itself (r=0·728).

Mirsky *et al.* (1974) have suggested that 'normalization' of blood velocity measurements may result in better functional indices. From Fig. 5d and 5e it will be seen that SV/MA was the most satisfactory normalized velocity measurement in the separation of the good from the bad ventricles, followed by SV/PV. These results support the hypothesis that severe impairment of LV function may be associated with a relatively good initial acceleration of blood in the aorta, which, however, is not sustained by the failing ventricle (Cross and Light, 1974). This results in a reduction of PV, and in particular SV, compared to MA.

The failing ventricle, through an increase in its end-diastolic volume, is capable of ejecting a normal or near-normal stroke volume despite a fall in its ejection fraction. This ventricular dilatation is theoretically advantageous in that each individual myocardial fibre needs to shorten less to expel the same quantity of blood (Burch, Ray, and Cronvich, 1952). This advantage is, however, offset by the increased wall tension that the dilated ventricle must develop in order to generate the same pressure within its cavity (application of Laplace's law to the ventricle—Burton, 1957). This increased wall tension results in increased myocardial oxygen demand. In a normal ventricle, which ejects at least 50 per cent of its end-diastolic volume, the change in wall radius is considerable. The decreasing radius offsets the increasing intracavitary pressure with the result that wall tension is not maintained at peak levels for long, but decreases early in the ejection phase. Dilatation of the LV with reduction of its ejection fraction means that higher wall tensions must be maintained for longer in order to eject the same stroke volume. The metabolic disadvantage of prolonged and increased wall tension, however, may result in failure to sustain the initial relatively good acceleration, as indicated by our findings in patients with poor LV function. One possible reason for this is that myocardial oxygen demand exceeds the available oxygen supply, particularly towards the latter part of systole. Such an explanation is in keeping with the results of cell fractionation and enzymatic analysis of left ventricular endomyocardial biopsies, showing a reduction in mitrochondrial oxidative enzyme activity in patients with poor myocardial function, together with evidence of enhanced anaerobic glycolysis in patients with congestive cardiomyopathy who have dilated ventricles (Peters *et al.*, 1975).

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Congenital heart disease in Down's syndrome

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Eighty cases of Down's syndrome were found among 1504 children with congenital heart disease under the age of 15 years. The most common cardiac anomaly, ventricular septal defect, was found in 49 per cent of the 80 cases studied, while the second most frequently encountered anomaly, common atrioventricular canal, was found in 15 per cent. Haemodynamic investigations of 24 cases of ventricular septal defect showed Eisenmenger's syndrome to be present in 10 cases; this seemed to appear at an earlier age in mongoloid children than in other children with ventricular septal defect. Right-to-left shunt was found in 5 out of 9 cases of common atrioventricular canal. Pulmonary hypertension was found in all of 24 cases of ventricular septal defect and in 7 of 9 cases of common atrioventricular canal. The cumulative survival up to 10 years was 64 per cent for girls and 49 per cent for boys. Death was most commonly the result of pulmonary complications which occurred in 22 out of the 34 patients who died.

The high incidence of congenital heart disease in Down's syndrome is well known, and many authors have published figures on the frequency with which congenital heart defects are found. These figures vary from 7 to 70 per cent (Berg, Crome, and France, 1960; Evans, 1950; Liu and Corlett, 1959; Rowe, 1962; Rowe and Uchida, 1961; Øster, 1953). The varying results of these studies may be because different groups of patients are not directly comparable. The incidence is highest in necropsy series and lowest in clinical groups, where special methods of investigation, such as heart catheterization, were not used. Mongolism occurs more often in Caucasians than in other races (Engle and Ehlers, 1968). Øster (1956) estimated the incidence to be 0·16 per cent among live births in a Danish study. Boesen *et al.* (1963) found the frequency of mongolism to be 4·7 per cent (29 patients) in a clinical study of 615 children with congenital heart disease.

Present study

This study was undertaken: 1) to obtain more information about the nature of heart defects associated with Down's syndrome, 2) to describe the haemodynamics in groups of patients with ventricular septal defects and common atrioventricular canal, and 3) to estimate the mortality and causes of death.

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Results

The clinical study includes 80 patients with Down's syndrome under the age of 15 years of age who were selected from a total of 1504 children with congenital heart disease. These patients were admitted to hospital in the department of paediatrics and the majority were investigated in the department of cardiology, at the University Hospital, Århus, Denmark, during the years 1963 to 1974. During this period a total number of 144 children with Down's syndrome were admitted, of whom 56 per cent had congenital heart disease.

Sex and age

The group of children studied comprised 41 girls and 39 boys. The youngest was 2 days and the oldest 12 years old at the time of admission to hospital. The mean age was 39 months, and 49 of the children (61%) were younger than 12 months.

Nature and frequency of cardiac malformations

A final classification of the congenital heart disease was made in 76 patients. Forty-eight cases were classified by heart catheterization, 19 by necropsy without previous heart catheterization, and 9 cases by physical examination alone. In the remaining 4 cases it was not possible to obtain an exact diagnosis by physical examination, and since these patients died later without subsequent necropsy, a final diagnosis could not be made.

The incidence of various major cardiovascular abnormalities is seen in Table 1. The largest group is ventricular septal defect (49%), and the next largest is common atrioventricular canal of the complete type (19%). The major cardiac malformations were accompanied by other cardiovascular lesions in several cases, as shown in Table 2.

TABLE 1 *Incidence of major cardiovascular malformations in 80 children with Down's syndrome: distribution of similar lesions in children in same age group (Keith et al., 1958) is shown for comparison*

Cardiac malformation	*This study*	*Keith* et al. (1958)
Ventricular septal defect	39 (49%)	25%
Common atrioventricular canal	15 (19%)	2%
Tetralogy of Fallot	6 (8%)	11%
Atrial septal defect	3* (4%)	7%
Persistent ductus arteriosus	5 (6%)	17%
Pulmonary stenosis	3 (4%)	7%
Primary pulmonary hypertension	2 (2%)	
Coarctation of aorta	1 (1%)	6%
Mitral stenosis and regurgitation	1 (1%)	
Vascular ring	1 (1%)	
No diagnosis	4 (5%)	
	80 (100%)	

*Two of these 3 patients had an ostium primum atrial septal defect. In the third the type was uncertain from the necropsy report (no catheterization).

Haemodynamics

The results of heart catheterization of patients with ventricular septal defect and common atrioventricular canal are shown in Tables 3, 4, and 5. The uncomplicated ventricular septal defects have been classified as described by Kidd *et al.* (1965) (shown to the left in Table 3 and in Table 5). Group 1 contains ventricular septal defects with a small shunt (pulmonary blood flow/systemic blood flow <2/1) and normal pulmonary vascular resistance. Group 2 comprises ventricular septal defects with moderate sized or large shunts (pulmonary blood flow/systemic blood flow >2/1) and the pulmonary vascular resistance varying from low to high. Group 3 is made up of ventricular septal defects with small shunts (pulmonary blood flow/systemic blood flow <2/1) and high pulmonary vascular resistance. Group 4 includes patients with right-to-left or mixed shunts and high pulmonary vascular resistance (Eisenmenger's syndrome). Heart catheterization was performed in 24 patients with ventricular septal defects (14 boys and 10 girls). The age of the children varied from 2 months to 140 months and the mean age was 54 months. Ten patients were found to have Eisenmenger's syndrome. Twenty-three patients had pulmonary hypertension (systolic pulmonary artery pressure >40 mmHg (5·3 kPa). In one case the pulmonary artery pressure could not be measured but the

TABLE 2 *Coexisting cardiac malformations in 67 children† with Down's syndrome and congenital heart disease*

Major cardiac malformation	*Coexisting cardiac malformations*				
	No. of cases	*Persistent ductus arteriosus*	*Atrial septal defect*	*Coarctation of aorta*	*Other lesions*
Ventricular septal defect	32	5	6	1	Malformation of tricuspid valve (1)
Common atrioventricular canal	15	1	1		Valvar pulmonary stenosis (1)
Atrial septal defect	3				
Primary pulmonary hypertension	2		1*		
Coarctation of aorta	1	1			
Vascular ring	1	1			Small ventricular septal defect (1)
Tetralogy of Fallot	6		1		
Persistent ductus arteriosus	5				
Pulmonary stenosis	2		1		
Total	67	8	10	3	3

†Only those patients in whom the nature of the cardiac abnormalities was determined by heart catheterization or necropsy are included in the Table.
*Pulmonary hypertension could not be attributed to the small atrial septal defect.

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TABLE 3 *Results of heart catheterization in 24 patients with Down's syndrome and ventricular septal defect*

*Group**	*Age*	*Sex*	*BSA* (m^2)	*Pressures (mmHg)*					*Systemic blood pressure*	*Pulmonary vascular resistance†* (*units*)	*Shunt*
				Right atrium	*Pulmonary artery*	*Right ventricle*	*Left ventricle*	*Aorta*			
1	6 yr	M	0·74	9/4	50/21	52/8	77/0–11			4	L→R 45%
2	1 yr 3 mth	M	0·42	6/0		65/3	64/3				L→R 52%
2	3 yr	M	0 46	0/–5	68/34	67/–4			125/80	6	L→R 65%
2	3 yr	M	0·52	8/0	80/35	77/7	95/10			20	Large L→R shunt
2	2 mth	F	0·20	14/3	59/19	66/8				22	L→R 66%
2	9 yr	F	0·95	10/3	69/44	68/8			80/40	4	L→R 58%
2	3 mth	F	0 22	5/2	42/17	48/3	55/0			14	L→R 57%
2	1 yr 3 mth	M	0·34	8/3	56/26	60/4		59/36		6	L→R 58%
3	5 yr	M	0·60	6/1	86/35	84/6	84/8			22	L→R 27%
3	5 mth	M	0·26	7/4	53/22	52/8		53/32		11	Small L→R shunt
3	5 yr	F	0·74	13/10	81/52	80/3		79/50		12	L→R 32%
3	7 yr	M	0 73		54/20	58/5	86/4			6	L→R 32%
3	2 yr	F	0 44	7/1	52/22	55/0	93/3			11	L→R 25%
3	7 mth	F	0·36	8/1	103/56	106/6			140/80	> 20	L→R 20%
4	4 yr	F	0 56	1/1	69/35	71/0			120/80	28	R→L 50%
4	11 yr	F	0·95	12/6	84/54	85/3		99/70		37	L→R 19% R→L 40%
4	8 yr	F	0 85	9/6	71/38	71/6	71/6			25	L→R 30% R→L 50%
4	9 yr	F	0 93	9/3	88/42	87/0	85/0			9	L→R 45% R→L 15%
4	8 mth	F	0 31	6/1	68/32	64/6	57/1–10	68/37		26	L→R 40% R→L 25%
4	2 yr	F	0·51	9/5	75/37	73/0–10		74/36		16	L→R 15% R→L 50%
4	10 yr	F	1·00	7/0	91/50	98/7			120/80	35	L→R 35% R→L 75%
4	10 yr	M	0·85	9/6	82/55	79/8		81/60		23	L→R 8% R→L 40%
4	3 yr	F	0·52	8/4	75/53	69/5	64/7			22	L→R 25% R→L 40%
4	6 mth	M	0 28	4/1–3	56/24	56/1	55/3			26	L→R 42% R→L 50%

Conversion from Traditional Units to SI Units: 1mm Hg≈0·133 kPa.
*Classification of Kidd *et al.* (1965).
†Pulmonary vascular resistance expressed in units (mm Hg/pulmonary blood flow in litres per minute).

right ventricular pressure was found to be raised, and angiocardiography did not show valvar pulmonary stenosis. In 9 patients the pulmonary hypertension was severe (pulmonary artery pressure >75 mmHg (10·0 kPa) systolic).

Heart catheterization was performed in 9 patients with common atrioventricular canal (Table 5). Five patients had right-to-left or mixed shunts, and 7 patients had pulmonary hypertension. There were 6 boys and 3 girls in the group, varying in age from 3 months to 106 months, with a mean age of 59 months.

TABLE 4 *Grouping of 24 cases of ventricular septal defect in Down's syndrome, and of 398 cases of ventricular septal defect (Kidd et al., 1965)*

	Kidd et al. (1965)	*This study*
*Group**	*No. of patients*	*No. of patients*
1	123 (31%)	1 (4%)
2	240 (60%)	7 (29%)
3	14 (4%)	6 (25%)
4	21 (5%)	10 (42%)
Total	398	24

*Classification of Kidd *et al.* (1965).

Operability and surgery

After heart catheterization the operability of all

TABLE 5 *Results of heart catheterization in 9 patients with Down's syndrome and common atrioventricular canal*

Age	*Sex*	*BSA (m²)*	*Pressures (mmHg)* Right atrium	Pulmonary artery	Right ventricle	Left ventricle	Aorta	*Pulmonary vascular resistance (units)*	*Shunt*
4 yr	M	0·71	14/6	30/16	66/5		67/40	3	No shunt
4 yr	M	0·69	8/5	15/9	87/4	87/4		4	R→L 80%
3 mth	F	0·19	8/4	53/27	57/3	58/2		>30	No significant shunt
1 yr 6 mth	M	0·44	19/7	100/59	100/17	104/15		?	Blood samples unreliable
8 yr	M	0·74	16/2	86/45	83/16	87/15		14	L→R 56% R→L 35%
7 yr	F	0·84	8/3	48/17	42/5	100/0		8	L→R 14%
10 yr	F	0·85	6/3	76/43	77/0		77/58	11	L→R 48% R→L 25%
6 yr	M	0·64	6/4	69/39	69/3	69/3		37	L→R 8% R→L 85%
4 mth	M	0·22	7/4	51/18	66/1	67/4		19	L→R 73% R→L 20%

Conversion from traditional units to SI units: 1 mmHg ≈ 0·133 kPa.

patients was assessed. The results are shown in Table 6. In 2 patients with ventricular septal defect operation was not recommended because of severe mental retardation. The parents refused operation for one case of persistent ductus arteriosus and for one case of atrial septal defect.

During the period of this study 16 operations were performed, but several patients are still waiting for surgery.

Mortality

Life expectancy tables up to age 10 years have been constructed for girls and boys, the children entering the tables at birth. Cumulative survival rates are shown in Tables 7 and 8, and illustrated in the Figure. The mortality is very high during the first year of life, with only 61 per cent of the boys and 71 per cent of the girls surviving this period. After one year of age the curve becomes flatter and after 10 years the cumulative survival for girls is 64 per cent and 49 per cent for boys. This study has shown no significant sex difference in the cumulative survival using the Mantel Haensel test (Ipsen and Feigl, 1970). (χ^2 1·14. P>0·2). The causes of death are shown in Table 9. Of 16 patients operated on, 6 have died, and of the 16 patients found inoperable at the time of heart catheterization, 2 have died.

Discussion

It has long been known that common atrioventricular canal and ventricular septal defect are common cardiac malformations in patients with Down's syndrome (Tandon and Edwards, 1973). Defects in the atrioventricular canal, atrial septal defects of the secundum type, and ventricular septal defects comprised 80 per cent of all cardiac malformations in a group of British patients evaluated at necropsy (Berg *et al.*, 1960). In the prospective study of Rowe and Uchida (1961), the most frequent anomaly was defect in the atrioventricular

TABLE 6 *Assessment of operability in 48 patients with Down's syndrome and congenital heart disease*

Cardiac anomaly	*No. of patients*	*Indication for operation*	*No indication for operation*	*Inoperable*
Ventricular septal defect	24	10	3	11
Common atrioventricular canal	9	3	3	3
Tetralogy of Fallot	5	5		
Persistent ductus arteriosus	5	5		
Atrial septal defect	2	2		
Primary pulmonary hypertension	2			2
Mitral stenosis and regurgitation	1		1	
Total	48	25	7	16

TABLE 7 *Life expectancy table for 41 girls with Down's syndrome and congenital heart disease*

Age interval (yrs)	*Alive at start of interval*	*Live withdrawals during interval*	*At risk of death during interval*	*Deaths during interval*	*Death rate*	*Survival rate*	*Cumulative survival rate*
0–1	41	0	41·0	11	0·27	0·73	1·00
1–2	30	2	29·0	1	0·03	0·97	0·73
2–3	27	0	27·0	0	0·00	1·00	0·71
3–4	27	0	27·0	0	0·00	1·00	0·71
4–5	27	2	27·0	0	0·00	1·00	0·71
5–6	25	2	24·0	1	0·04	0·96	0·71
6–7	22	2	21·0	0	0·00	1·00	0·68
7–8	20	1	19·5	0	0·00	1·00	0·68
8–9	19	2	18·0	0	0·00	1·00	0·68
9–10	17	2	16·0	1	0·06	0·94	0·68
10–11	14	3	12·5	1	0·08	0·92	0·64

TABLE 8 *Life expectancy table for 39 boys with Down's syndrome and congenital heart disease*

Age interval (yrs)	*Alive at start of interval*	*Live withdrawals during interval*	*At risk during interval*	*Deaths during interval*	*Death rate*	*Survival rate*	*Cumulative survival rate*
0–1	39	1	38·5	15	0·39	0·61	1·00
1–2	23	0	23·0	0	0·00	1·00	0·61
2–3	23	3	21·5	0	0·00	1·00	0·61
3–4	20	1	19·5	0	0·00	1·00	0·61
4–5	19	0	19·0	0	0·00	1·00	0·61
5–6	19	3	17·5	2	0·11	0·89	0·61
6–7	14	2	13·0	0	0·00	1·00	0·54
7–8	12	3	10·5	1	0·10	0·90	0·54
8–9	8	4	6·0	0	0·00	1·00	0·49
9–10	4	1	3·5	0	0·00	1·00	0·49
10–11	3	2	1·5	0	0·00	1·00	0·49

TABLE 9 *Cause of death in 34 patients with Down's syndrome and congenital heart disease*

Cardiac anomaly	*Pulmonary complications*	*Cardiac failure*	*Gastroenteritis Peritonitis*	*Other reasons*
Ventricular septal defect	7 (1 postoperative)	3	2	Cerebral abscess 1
Common atrioventricular canal	8			Operation 1
Tetralogy of Fallot	1			Thrombosis of left pulmonary artery (2 months after Blalock operation) 1
Persistent ductus arteriosus				Postoperative (cause unknown) 1
Stenosis of pulmonary valve	1			
Atrial septal defect	1			
Coarctation of aorta			1	
Mitral stenosis and regurgitation				Accident occurring at home 1
Vascular ring	1			
No diagnosis	3	1		
Total	22	4	3	5

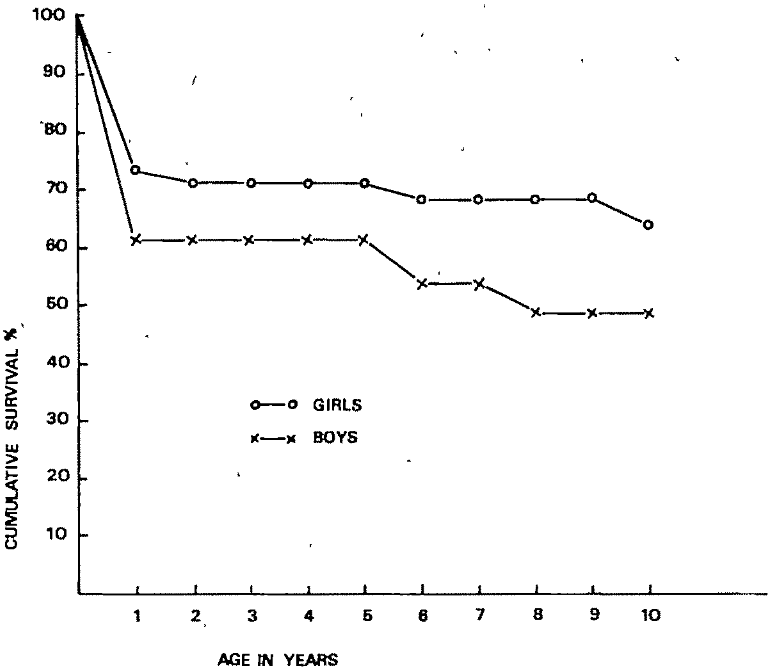

FIG. *Cumulative survival for first 10 years of life in 41 girls and 39 boys with congenital heart disease and Down's syndrome.*

canal (36%), and ventricular septal defects were found in 33 per cent. Our results are similar to those of other workers. Table 1 shows the figures of Keith, Rowe, and Vlad (1958) describing children with congenital heart disease in the same age group as the patients in this study. The most striking differences are that ventricular septal defect is more frequent and common atrioventricular canal much more frequent in Down's syndrome. In the present investigation 28 coexisting cardiovascular malformations were found in 67 patients. However, there is no reason to believe that this figure differs from that found in non-mongoloid children with congenital heart disease (Berg *et al.*, 1960).

Few haemodynamic investigations in patients with Down's syndrome and congenital heart disease have been published (Chi and Krovetz, 1975; Kreutzer *et al.*, 1973; Liu and Corlett, 1959; Shaher *et al.*, 1972; Soudon *et al.*, 1975). Though pulmonary hypertension and Eisenmenger's syndrome have been known to occur in mongolism the exact incidence is difficult to assess. This study shows that a greater number of ventricular septal defects than would be expected (Kidd *et al.*, 1965) fall into groups 3 and 4 (Eisenmenger's syndrome), and only a small portion into group 2, which in non-mongoloid children is the largest group (Table 4). It may be argued that this difference results from the high proportion of patients with associated cardiovascular malformations in this series. Excluding such cases, the total number is reduced to 13, but the distribution of patients in the different groups is not essentially altered, 4 cases (31%) falling in group 4 and 4 cases in group 3. No cases of Eisenmenger's syndrome were found in the study of Kidd *et al.* (1965) before the age of 2 years, while in the present study 2 cases were diagnosed at an earlier age (viz. 6 and 8 months). Shaher *et al.* (1972) also found that 76 per cent of patients with Down's syndrome and ventricular septal defect or common atrioventricular canal (10 out of 13 patients) had Eisenmenger's syndrome (patients with right-to-left or bidirectional shunts). If such patients are included in the present material, the total number of Eisenmenger's syndrome would be 45 per cent (15 of 33 patients). Thus, our data confirm the observation that more patients with Down's syndrome and ventricular septal defect develop Eisenmenger's syndrome than do non-mongoloid children with the same cardiac anomaly and that this occurs at an earlier age. In this study pulmonary hypertension was found in all 24 cases of ventricular septal defect and in 7 of 9 cases of common atrioventricular canal. These findings are in accordance with those of Soudon *et al.* (1975) who found an earlier and greater increase of pulmonary vascular resistance in mongoloid children with ventricular septal defect (10 patients) than in non-mongoloids. Chi and Krovetz (1975) found that the mean pulmonary artery pressure was raised in 20 of 24 patients with Down's syndrome and ventricular septal defect. If patients with Down's syndrome who have ventricular septal defects or common atrioventricular canal are considered for surgical correction, it is recommended that they undergo cardiac catheterization at an earlier age than non-mongoloid children. The early surgery might then prevent the development of pulmonary vascular disease and right-to-left or mixed shunt. It is possible that the pulmonary vessels in mongoloid children are more sensitive to raised pressure in the pulmonary circulation than those of non-mongoloid children, though Plett, Tandon, and Moller (1974) could not find any major histological difference between pulmonary vessels in patients with common atrioventricular canal and mongolism and those in patients without mongolism. Thus, pulmonary hypertension in these children is not adequately understood, and more investigations are needed.

The results of the present investigation, which includes operated and unoperated patients, show a higher survival rate at 10 years than in the investigation of Fabia and Drolette (1970), who found 45 per cent of the boys and 32 per cent of the girls with Down's syndrome and congenital heart disease surviving the first 10 years of life, while 75 per cent of the patients without congenital heart disease were alive at the age of 10 years. The observed difference in mortality may be the result of a disparity in the selection of patients in the 2 studies, as no information is given about the types of congenital heart disease in Fabia and Drolette's series, and there may have been more serious malformations than in the present study. In our series, there was a lower mortality in females, whereas Fabia and Drolette reported a significantly lower survival rate for females from age 2 upwards.

Table 9, which lists the causes of death, shows that 22 of the 34 patients died from pulmonary complications. Infection in the respiratory tract is a common complication in patients with Down's syndrome, both with and without congenital heart disease. Liu and Corlett (1959) showed that in 19 of 22 mongoloid children without congenital heart disease death was the result of pulmonary complications.

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Constancy of pressure-rate product in pacing-induced angina pectoris

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The pressure-rate product during anginal pain produced by right atrial pacing was studied in 12 patients before, during, and after an angiotensin infusion sufficient to produce a significant rise in blood pressure. During the infusion the pain occurred at a significantly lower heart rate ($P<0.001$). However, the pressure-rate product was similar during anginal pain before and during the angiotensin-induced hypertension and after it wore off. Our studies support the concept that in each individual there is a constant level of myocardial oxygen consumption, as expressed by the pressure-rate product, at which anginal pain occurs.

Constancy of the pressure-rate product (heart rate × systolic blood pressure) or the triple product (heart rate × systolic blood pressure × ejection time) at the onset of exercise-induced pain has been observed in patients with exertional angina (Robinson, 1967; Redwood *et al.*, 1971). Both 'products' reflect myocardial oxygen consumption ($M\dot{V}O_2$). The duration of the ejection time is now thought to be of minor importance in estimating $M\dot{V}O_2$. The tension-time index has been found to correlate less well with $M\dot{V}O_2$ than the pressure-rate product or just the heart rate (Monroe, 1964; Kitamura *et al.*, 1972; Sheffield and Roitman, 1973; Nelson *et al.*, 1974).

It has been shown that with either exercise or atrial pacing patients develop ischaemic manifestations at a constant tension-time index (Sowton *et al.*, 1967; Bahler and Macleod, 1971) or pressure-rate product (O'Brien *et al.*, 1969). We have further investigated the constancy of the pressure-rate product in patients who developed anginal pain with rapid right atrial pacing.

Patients and methods

Twelve patients were studied. All had developed anginal chest pain in response to rapid right atrial pacing performed by the usual technique (Sowton *et al.*, 1967; Kelemen *et al.*, 1973). Atropine was given to three patients to reverse second degree atrioventricular block occurring at lower heart rates (Cokkinos *et al.*, 1973). All were premedicated with 5 to 10 mg diazepam intramuscularly. Blood pressure during the test was directly recorded in eight patients through an indwelling needle in the brachial artery and measured by a cuff sphygmomanometer in the remaining four patients. The pressure-rate product at the onset of pain was calculated in mmHg/min (Sheffield and Roitman, 1973) (1 mmHg/min=0·133 kPa/min).

After pacing in the initial test had been stopped an intravenous infusion of angiotensin (2·5 mg in 1 litre normal saline) was started together with continuous monitoring of the blood pressure. When the systolic pressure had increased by 20 mmHg (2·7 kPa) or more rapid right atrial pacing was repeated and the pressure-rate product at the time of anginal pain was noted. After the angiotensin infusion had been stopped and the blood pressure had returned to initial levels pacing was repeated and the pressure-rate product at the onset of anginal pain recorded again. The heart rate, blood pressure, and pressure-rate product at the time of anginal pain before, during, and after angiotensin administration were compared by the paired *t* test.

Informed consent for the addition of an angiotensin infusion to the usual procedure of diagnostic rapid atrial pacing was obtained from all patients.

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Results

Angiotensin produced the desired increase in systolic blood pressure in all 12 patients (see Table). The cardiac frequency at which each patient developed chest pain was significantly higher before and after the effect of the angiotensin wore off and lower during the infusion ($P<0.001$). Thus, though there was a large rise in systolic pressure during angiotensin infusion, the fall in heart rate

TABLE *Heart rate, blood pressure, and pressure-rate product at onset of anginal pain in patients subjected to right atrial pacing before, during, and after angiotensin infusion*

Case No.	Sex	Age	*A* *Before angiotensin*			*B* *During angiotensin*		
			HR (min)	*BP mmHg (kPa)*	*PRP mmHg/min (kPa×10³/min)*	*HR (min)*	*BP mmHg (kPa)*	*PRP mmHg/min (kPa×10³/min)*
1*	M	54	158	120/90 (15·96/11·97)	18 96 (2 52)	125	165/110 (21·94/14·63)	20 62 (2·74)
2*	M	68	165	150/90 (19·95/11·97)	24 75 (3·29)	140	170/100 (22 61/14 63)	23 80 (3 16)
3	M	51	175	165/100 (21·94/13·30)	28·87 (3·83)	148	190/130 (25 27/17·29)	28 12 (3·73)
4*	M	60	165	140/180 (18 62/10·64)	23 07 (3 06)	110	200/110 (26 60/14·63)	22·00 (2·92)
5*	M	47	152	150/90 (19 95/11·97)	21·02 (2·79)	125	175/120 (23·27/15·96)	21 87 (2 90)
6*	M	52	187(A)	136/80 (18 08/10·64)	25 43 (3·38)	140	190/110 (25 27/14 63)	26 60 (3·53)
7	M	44	160(A)	145/80 (19·28/10·64)	23·20 (3 08)	130	180/110 (23·94/14 63)	23·40 (3 11)
8*	M	62	175	135/85 (17·95/11 30)	23·62 (3 14)	130	180/105 (23 94/13·96)	23 40 (3 11)
9	F	54	166	140/90 (18 62/11·97)	23 24 (3·09)	135	175/100 (23·27/13 50)	23·62 (3·14)
10*	M	60	150(A)	125/80 (16 62/10·64)	18 75 (2·49)	120	160/105 (21·28/13 96)	19·20 (2·55)
11*	M	48	180	130/75 (17·29/9·97)	23 40 (3·11)	140	172/110 (22 87/14·63)	24·08 (3 20)
12*	M	61	156	135/80 (18·52/10 64)	21 06 (2 80)	130	160/100 (21·28/13·30)	20·80 (2·76)
Mean (±SEM)			165·7 (±3·31)	139 3/84 (±3·20 (systolic))	22 94 (±0 80) (0 10)	131 0 (±2 99)	176·4/109·1 (±4·01 (systolic))	23·12 (±0 72) (0 09)
A vs B						Δ34 7 SED±2 82 P<0·001	Δ37 1 (systolic) SED±3·36 P<0·001	Δ0 18 SED±0·24 P>0·05
B vs C								
A vs C								

*Ischaemic ST segment changes during pain.
Abbreviations: HR=heart rate; BP=blood pressure; PRP=pressure-rate product; SEM=standard error of mean; SED=standard error of difference; Δ=difference.

was such that the product of rate and pressure was almost exactly the same. The heart rate and blood pressure at the onset of pain were not significantly different before and after angiotensin (P>0·05).

Ten of our patients developed ischaemic ST segment changes at the time of anginal pain (see Fig.). No untoward reactions to angiotensin were noted. Its hypertensive effect wore off in 4 to 11 (mean 6·9) minutes.

Discussion

Our results support the hypothesis that there is a constant myocardial oxygen consumption for each patient at which angina will develop. Each of our patients experienced anginal pain at a constant pressure-rate product regardless of whether this was produced by a relatively greater increase of the heart rate or of the systolic blood pressure.

We chose atrial pacing and angiotensin infusion

C *After angiotensin*			*Angiotensin effect ceased after: (min)*
HR (min)	*BP mmHg (kPa)*	*PRP mmHg/min (kPa × 10³/min)*	
160	118/80 (15·69/10·64)	18·88 (2·51)	5·5
160	150/100 (19·95/13·30)	24·00 (3·19)	4·0
170	170/100 (22·61/13·30)	28·90 (3·84)	8·5
170	130/100 (17·29/13·30)	22·10 (2·93)	6·5
160	140/95 (18·62/12·63)	22·40 (2·97)	10·0
180	140/80 (18·62/10·64)	25·20 (3·35)	11·0
155	148/90 (19·68/11·97)	22·94 (3·05)	5·5
180	130/90 (17·29/11·97)	23·40 (3·11)	4·5
160	142/85 (19 68/11·30)	22 72 (3·02)	6·5
150	120/80 (15·96)/10·64	18·00 (2·39)	6·0
170	128/70 (17·02/9·31)	22·40 (2·97)	7·0
158	130/75 (17·29/9·97)	20·54 (2·73)	8·0
164·8 (±2·85)	137·1/88·7 (±4·17 (systolic))	22·62 (±0·819)	6·9
Δ33·8 SED ±3·14 P < 0·001	Δ39·3 SED ±2·92	Δ0·50 SED ±0·31 P > 0·05	
Δ0·9 SED ±1·06 P > 0·05	Δ2 2 SED ±2·16 P > 0·05	Δ0·32 SED ±0·30 P > 0·05	

for manipulating the pressure-rate product for various reasons. Rapid pacing, in contrast to muscular exercise (Piggott *et al.*, 1971), does not produce any significant change in adrenergic activity provided diazepam is given to prevent undue anxiety (Voridis *et al.*, 1974). Nevertheless, Nelson *et al.* (1974) found that the pressure-rate product correlated very well with M$\dot{V}$O$_2$ in exercising patients. We chose angiotensin for raising the blood pressure because, in contrast to sympathomimetic pressor amines, it does not alter myocardial contractility in man (Ross and Braunwald, 1964; Perloff, Binnion, and DeLeon, 1967), though Koch-Weser (1964) and Fowler and Holmes (1964) have described a positive inotropic effect in animals. Moreover, venous tone, venous return, and heart volume, which are considered to influence M$\dot{V}$O$_2$ (Simaan, 1974), are only minimally affected by angiotensin (Rose *et al.*, 1962). Patients exercising after nitroglycerin develop anginal pain at a higher pressure-rate product than controls, presumably because of reduced ventricular dimensions, which lower the M$\dot{V}$O$_2$. Conversely, after propranolol the pressure-rate product at the onset of angina is reduced, possibly as the result of increased ventricular size, which tends to augment M$\dot{V}$O$_2$ (Wolfson, Phillips, and Schecter, 1970; Detry and Bruce, 1971; Goldstein and Epstein, 1973; Nelson *et al.*, 1974).

Angiotensin has been found to increase coronary arterial resistance (Fowler and Holmes, 1964) but Perloff *et al.* (1967) believed this action to be of no practical significance. Angiotensin has also been used to evaluate contractility in patients with coronary artery disease without any evidence of coronary constrictive effect (Parmley *et al.*, 1975). Anginal chest pain was taken as the criterion of a positive response to atrial pacing. It has been repeatedly stressed that ST segment changes are not specific enough, especially at high atrial pacing rates (Kelemen *et al.*, 1973; Rios and Hurwitz, 1974). Nevertheless, 10 of our 12 patients developed such changes coincidentally with the pain.

Our observations suggested that in addition to other possible haemodynamic modifications drugs preventing increases in blood pressure during exercise may be expected to ameliorate exertional angina.

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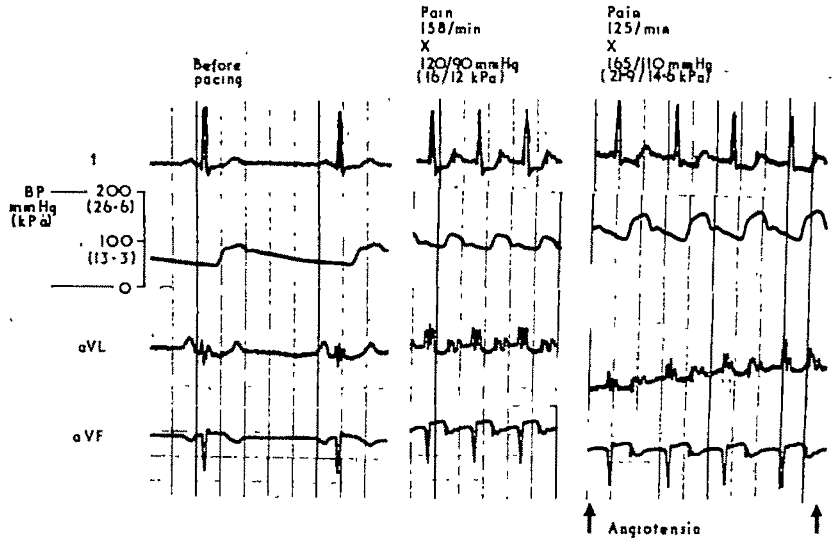

FIG. *Case 1. Anginal pain and ischaemic ST changes occur at about the same pressure-rate product before and after angiotensin administration.*

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Usefulness of systolic time intervals in differential diagnosis of constrictive pericarditis and restrictive cardiomyopathy[1]

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Systolic time intervals in 15 patients with constrictive pericarditis and seven patients with restrictive cardiomyopathy were compared in order to assess their value in the differential diagnosis of the two disorders. Clinical examination had failed to make the distinction. Right heart catheterization was helpful in diagnosing restriction but failed to differentiate patients with constrictive pericarditis from those with restrictive cardiomyopathy. The systolic time intervals clearly separated the two groups. The PEP/LVET was normal in all patients with constrictive pericarditis ($0{\cdot}34 \pm 0{\cdot}01$) and abnormal in all patients with restrictive cardiomyopathy ($0{\cdot}70 \pm 0{\cdot}09$, $P < 0{\cdot}001$). In 13 patients (five with restrictive cardiomyopathy and eight with constrictive pericarditis) the results of quantitative left ventricular angiocardiography were available. A high correlation ($r = -0{\cdot}90$, $P < 0{\cdot}01$) between the PEP/LVET and the ejection fraction confirmed the validity of the PEP/LVET as a measure of left ventricular performance in these patients. Thus the systolic time intervals clearly distinguished between constrictive pericarditis and restrictive cardiomyopathy and are a reliable non-invasive technique for making the difficult differential diagnosis.

Restrictive cardiomyopathy may simulate constrictive pericarditis both clinically and haemodynamically (Hetzel, Wood, and Burchell, 1953; Gunner *et al.*, 1955; Clark, Valentine, and Blount, 1956; Goodwin *et al.*, 1961; Wasserman *et al.*, 1962; Burch and Phillips, 1962; Parry and Abrahams, 1963; Shabetai, Fowler, and Fenton, 1965; Ramsey *et al.*, 1970). Whereas diastolic filling of the ventricle is severely impaired in both diseases probably the systolic performance differs. The systolic time intervals are usually normal in constrictive pericarditis (Armstrong, Lewis, and Gotsman, 1973; Lewis and Gotsman, 1973), but they are a sensitive indicator of abnormal left ventricular performance in cardiomyopathy (Weissler, Harris, and Schoenfeld, 1968, 1969; Lewis *et al.*, 1973). Therefore we have reviewed our cases of these two disorders to see whether systolic intervals might provide a reliable non-invasive method of distinguishing one from the other.

Patients and methods

Fifteen patients with constrictive pericarditis and seven with restrictive cardiomyopathy were selected for study. All the patients were symptomatic. At the time of study they were receiving no medication. All underwent right heart catheterization, and left heart catheterization with left ventriculography was performed in 13. The systolic time intervals were routinely obtained the day before catheterization.

The clinical profile of the 15 constrictive pericarditis patients was typical. All underwent successful pericardectomy. None had visible pericardial calcification. The seven patients with restrictive cardiomyopathy were clinically indistinguishable from those with constrictive pericarditis. All presented the strict criteria of restrictive physiology (Fowler, 1971). None had obstructive or purely congestive cardiomyopathy, in which the restrictive features may develop late in the course of the disease. In four of the seven patients the diagnosis was confirmed by finding a normal pericardium at thoracotomy. Another patient had endomyocardial fibroelastosis, confirmed at necropsy, and another had haemochromatosis. The aetiology of the restrictive cardiomyopathy in the remaining patient was not established but his subsequent clinical course was highly suggestive of cardiomyopathy.

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Systolic time intervals were determined by our usual methods (Lewis *et al.*, 1974). In the 13 patients who underwent left heart catheterization and cineventriculography left ventricular volumes were determined from the RAO projection by the area-length method (Sandler and Dodge, 1968; Kasser and Kennedy, 1969). All statistical evaluations were made using standard statistical methods.

Results

The results of right heart catheterization in the two groups of patients are shown in Table 1. All pressures were raised in both groups and the pressure pulses were typical of restriction. There were no significant differences between the pressures for each group except for the pulmonary artery diastolic pressure, which was slightly higher in the cases of restrictive cardiomyopathy. Notably the mean pulmonary wedge pressure was not significantly different from the mean right atrial pressure in either group. The respiratory variation of peak arterial pressure was slightly greater than normal in each group but did not differ between the groups. The cardiac index was normal in the patients with constrictive pericarditis but was below normal and significantly different in the restrictive cardiomyopathy group.

TABLE 1 *Right heart catheterization results (means ± SEM)*

	Constrictive pericarditis (n=15)	*Restrictive myocardopathy (n=7)*	*P*
RA mean (mm Hg)	13±1	16±2	NS
RVEDP (mm Hg)	13±1	17±2	NS
PADP (mm Hg)	15±1	20±2	<0·05
PCW (mm Hg)	16±2	20±2	NS
Arterial pulse pressure (mm Hg)	17±5	16±4	NS
Cardiac index (l/min per m²)	3·2±0·3	2·3±0·2	<0·05

RA=right atrium; RVEDP=right ventricular end-diastolic pressure; PADP=pulmonary artery end-diastolic pressure; PCW=pulmonary capillary wedge pressure.

Conversion from Traditional to SI Units: 1mm Hg≈0·133 kPa.

The systolic time intervals are shown in Table 2. The mean values for the QS_2I, LVETI, PEPI, and PEP/LVET of the two groups were all significantly different. The PEP/LVET was normal in the constrictive pericarditis cases but highly abnormal in those of restrictive cardiomyopathy. The QS_2I was normal in the restrictive cardiomyopathy group but significantly short in the cases of constrictive pericarditis.

The Fig. shows the relation between the left ventricular ejection fraction and the PEP/LVET in five patients with restrictive cardiomyopathy and eight with constrictive pericarditis. A high correlation was present ($r=-0{\cdot}90$, $P<0{\cdot}01$). It is also clear that all constrictive pericarditis patients had a normal ejection fraction (0·68±0·02) while the ejection fraction was abnormal in all patients with restrictive cardiomyopathy (0·42±0·08, $P<0{\cdot}005$).

Discussion

The similarity of the clinical and haemodynamic data in the two groups of patients was expected. The characteristic intracardiac pressures and pulse configurations first described by Bloomfield *et al.* (1946) and further defined by others later (Hansen, Eskildsen, and Götzsche, 1951; McKusick, 1952; Yu *et al.*, 1953; Wilson *et al.*, 1954) are now known not to be pathognomonic of constrictive pericarditis (Wilson *et al.*, 1954; Lyons, Zuhdi, and Kelly, 1955; Burwell and Robin, 1954; Balchum, McCord, and Blount, 1956). That was so in our series. While the total clinical picture may permit the proper diagnosis, many cases have been reported in which primary myocardial disease masqueraded as constrictive pericarditis (Hetzel *et al.*, 1953; Gunner *et al.*, 1955; Clark *et al.*, 1956; Wasserman *et al.*, 1962; Burch and Phillips, 1962; Parry and Abrahams, 1963; Burwell and Robin, 1954). Among these so-called restrictive cardiomyopathies are endocardial fibroelastosis (Clark *et al.*, 1956; Parry and Abrahams, 1963), cardiac amyloidosis (Hetzel *et al.*, 1953; Gunner *et al.*, 1955), cardiac haemochromatosis (Wasserman *et al.*, 1962), and idiopathic myocardial fibrosis (Hetzel *et al.*, 1953; Burch and Phillips, 1962; Burwell and Robin, 1954).

Certain radiographic and angiographic techniques have been used to discriminate between these two conditions (Figley and Bagshaw, 1957; Steinberg, von Gall, and Finby, 1958; Preger *et al.*, 1965; Desilets, Grollman, and MacAlpin, 1966). The cineangiographic demonstration of a diastolic ventricular snap has not proved specific for constriction (Ramsey *et al.*, 1970; Desilets *et al.*, 1966). Angiographic measurement of cardiac wall thickness as an indication of pericardial thickening is unreliable since it does not clearly distinguish between chamber wall hypertrophy, pericardial effusion, and pericardial thickening (Figley and Bagshaw, 1957). The presence of pericardial calcification alone

TABLE 2 *Systolic time interval results (means ± SEM)*

Group	*No.*	*Age*	*QS_2I*	*LVETI*	*PEPI*	*PEP/LVET*
Constrictive pericarditis	15	40 ± 4	520 ± 6	401 ± 4	122 ± 3	0·34 ± 0·01
Restrictive cardiomyopathy	7	39 ± 5	545 ± 11	379 ± 5	171 ± 11	0·70 ± 0·09
P		NS	< 0·05	< 0·005	< 0·001	< 0·001

QS^2I = total electromechanical systole corrected for heart rate; LVETI = left ventricular ejection time corrected or heart rate; PEPI = pre-ejection period.

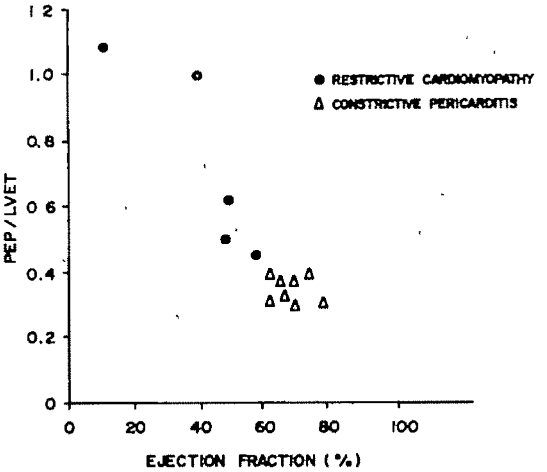

FIG. *Relation between the PEP/LVET and left ventricular ejection fraction in eight patients with constrictive pericarditis and five with restrictive cardiomyopathy. Correlation of –0·90 (P < 0·01).*

is not in itself enough to warrant a diagnosis of constrictive pericarditis (Harvey *et al.,* 1953). Calcification cannot be detected radiographically in at least 40 per cent of patients with constrictive pericarditis (Shabetai *et al.,* 1965). Clearly it is often impossible to distinguish between constrictive pericarditis and restrictive cardiomyopathy by standard diagnostic methods and the diagnosis has been made only by exploratory thoracotomy. Indeed, this was the case in four of our seven patients with restrictive cardiomyopathy. In retrospect, the PEP/LVET was abnormal in all of them and could have aided in the proper diagnosis.

Left ventricular performance in cardiomyopathy is usually significantly abnormal, resulting in a low ejection fraction and an abnormal PEP/LVET (Weissler *et al.,* 1968, 1969; Lewis *et al.,* 1973, 1974). Seemingly systolic performance is nearly always preserved in constrictive pericarditis. This was so in our patients and also in others previously reported (Armstrong *et al.,* 1973; Lewis *et al.,* 1973), despite subepicardial fibrosis being reported in some patients with advanced constrictive pericarditis (Dines, Edwards, and Burchell, 1958; Levine, 1973). Indeed, in a recent large series studied by Lewis *et al.* (1973) all 30 patients with constrictive pericarditis had a normal ejection fraction and PEP/LVET despite reduced left ventricular volumes.

The reduced QS_2I characteristic of the constrictive pericarditis patients in this series is not seen in patients with other types of chronic myocardial disease who are not on drugs (Weissler *et al.,* 1968). It was not noted in our restrictive cardiomyopathy group of patients. A shortened QS_2I, reported in patients with acute myocardial infarction or patients in the first few weeks after cardiac surgery, has been shown to be related to excessive adrenergic activity (Lewis *et al.,* 1972; Boudoulas *et al.,* 1973). Possibly chronic adrenergic hyperactivity is present in patients with constrictive pericarditis. Unlike patients with cardiomyopathy, they have a relatively normal left ventricular myocardium. Consequently they seem to respond to such a stimulus (Nakhjavan and Goldberg, 1970). As a result a normal cardiac output and ejection fraction are maintained despite the impaired diastolic filling. For reasons that are not clear the chronically diseased left ventricle usually shows catecholamine depletion in spite of increased adrenergic activity (Chidsey, Braunwald, and Morrow, 1965). Perhaps this explains the lack of QS_2I shortening in chronic myocardial disease. This possibility requires further investigation.

Our study has not shown whether the sharp difference in the systolic time intervals in constrictive pericarditis and restrictive cardiomyopathy would exist in milder forms of these disorders. Very probably the systolic intervals would be normal in mild constrictive pericarditis, and also possibly in early cases of restrictive cardiomyopathy. Nevertheless, in patients with clinically severe systemic congestion measurement of the systolic time intervals seems a valuable, noninvasive way of differentiating between cases of constrictive pericarditis and restrictive cardiomyopathy.

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Systolic time intervals in the differential diagnosis of constrictive pericarditis and cardiomyopathy

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Systolic time intervals (STI) were measured from simultaneously recorded phonocardiograms, carotid pulse tracings, and electrocardiograms in 11 patients with constrictive pericarditis and in 10 patients with cardiomyopathy to assess the value of STI in the differential diagnosis of the two conditions. The predicted ejection fraction was calculated from the STI. The results were compared and found significantly different in the two groups of patients. The ratio PEP/LVET and the ejection fraction were found to have greater discriminatory values and separated the two groups clearly.

Measurement of STI, a simple, noninvasive bedside technique, appears to be useful in distinguishing between constrictive pericarditis and cardiomyopathy.

Clinical differentiation between constrictive pericarditis and cardiomyopathy, particularly the constrictive or the restrictive variety, is often difficult. Even sophisticated procedures like cardiac catheterization and angiocardiography may not yield a definite diagnosis and surgical exploration is sometimes necessary. Measurement of systolic time intervals (STI) is a simple, noninvasive bedside technique for assessing the left ventricular performance.

In myocardial dysfunction such as in cardiomyopathy there is reduced myocardial contractile performance leading to a decrease in the maximal rate of rise in isovolumetric pressure which results in prolongation of the pre-ejection period (PEP) and a reduced rate of myocardial fibre shortening and thus a decrease in stroke volume and ejection fraction. In constrictive pericarditis, on the other hand, the basic problem is one of impaired filling rather than of emptying, with normal or near normal systolic contraction and ejection fraction. This basic physiological difference prompted us to study the STI in these two disorders to assess their value in differential diagnosis.

Patients and methods

Studies were made in 11 patients with chronic constrictive pericarditis, proved by cardiac catheterization and surgery in all but two patients, and in 10 patients with cardiomyopathy with typical clinical and haemodynamic features.

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Fig. 1 shows the method of measuring the STI simultaneously from a phonocardiogram, carotid pulse tracing, and electrocardiogram recorded on a Gallileo three-channel, direct-writing recorder at a paper speed of 100 mm/s. A crystal microphone for recording the heart sounds was placed at a site over the praecordium which prior auscultation had shown to be the best for recording the aortic component of the second heart

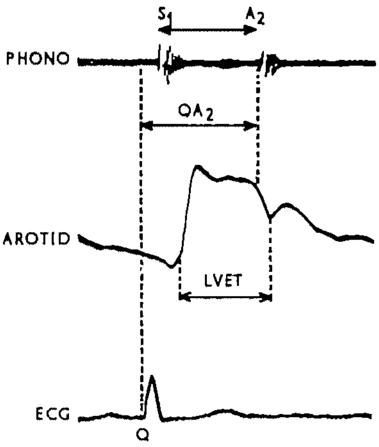

FIG. 1 *Measurement of systolic time intervals from simultaneous phonocardiagram, carotid pulse tracing and electrocardiogram.*

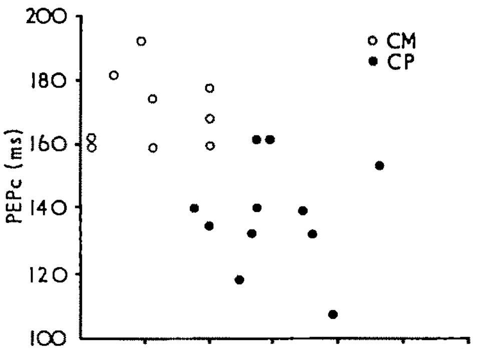

FIG. 2 *Relation between pre-ejection period (PEPc) and left ventricular ejection time (LVETc) in constrictive pericarditis and cardiomyopathy.*

sound. The right carotid arterial pulse was recorded with a funnel-shaped pick-up attached by a polyethylene tubing to a piezo-electric crystal microphone. The electrocardiographic lead, usually lead II, that clearly showed the Q wave was selected. The time intervals were calculated as the mean value from at least 10 cardiac cycles.

Left ventricular ejection time (LVET) was measured from the onset of the carotid upstroke to the incisura of the dicrotic notch. Pre-ejection period (PEP) was measured indirectly by subtracting left ventricular ejection time from the total electromechanical systole (Q-A_2): thus PEP$=$QA$_2$-LVET. The measurements of PEP and LVET were corrected for heart rate and sex by using the regression equation of Weissler, Harris, and Schoenfeld (1968). PEP/LVET ratio was calculated which was not significantly influenced by heart rate and sex. The predicted ejection fraction (EF) was calculated from the systolic time intervals by the regression equation of Garrard, Weissler, and Dodge (1970).

Routine right and left heart catheterization were performed in all the patients.

Results

The haemodynamic findings in the 11 cases of constrictive pericarditis are shown in Table 1. The cardiac index was normal, with low stroke volume and stroke work, in most of the patients. The left ventricular and right ventricular end-diastolic pressures were raised and nearly equal with a diastolic plateau.

The haemodynamic findings in the 10 cases of cardiomyopathy (Table 2) show a low or low normal cardiac index, low stroke volume and stroke work,

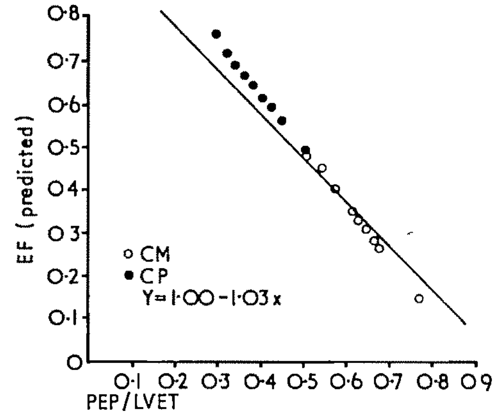

FIG. 3 *Relation between PEP/LVET ratio and ejection fraction (EF) in constrictive pericarditis and cardiomyopathy.*

TABLE 1 *Haemodynamic findings in 11 patients with constrictive pericarditis*

Case No.	*Age (years)*	*CI (l/min per m²)*	*SV (ml/beat)*	*LVEDP (mm Hg)*	*PCWP (mm Hg)*	*MPAP (mm Hg)*	*RVEDP (mm Hg)*	*MRAP (mm Hg)*	*LVSW (g–m)*
1	18	2·6	27	33	30	35	33	28	18·3
2	17	3·0	34	25	24	27	25	17	24·0
3	12	3·2	21	25	22	28	22	20	27·1
4	12	3·8	30	25	19	19	19	15	21·2
5	26	2·0	23	35	22	31	20	22	14 0
6	59	3·0	68	20	18	33	20	14	61·9
7	25	4·5	59	22	25	22	20	19	53·7
8	17	3·0	53	27	21	30	27	16	46·8
9	30	4·6	60	28	28	36	28	21	46·5
10	15	3·7	35	25	24	31	25	21	29·9
11	35	2·1	28	—	25	30	30	25	—

CI=cardiac index; SV=stroke volume; LVEDP=left ventricular end-diastolic pressure; PCWP=pulmonary capillary wedge pressure; MPAP=mean pulmonary artery pressure; RVEDP=right ventricular end-diastolic pressure; MRAP=mean right atrial pressure; LVSW=left ventricular stroke work.
Conversion from Traditional Units to SI Units: 1mm Hg ≈ 0.133 kPa.

TABLE 2 *Haemodynamic findings in 10 patients with cardiomyopathy*

Case No.	*Age (years)*	*CI (l/min per m²)*	*SV (ml/beat)*	*LVEDP (mm Hg)*	*PCWP (mm Hg)*	*MPAP (mm Hg)*	*RVEDP (mm Hg)*	*MRAP (mm Hg)*	*LVSW (g–m)*
1	35	2·4	42	5	7	16	2	7	42·2
2	32	1·5	30	15	15	29	12	7	29·0
3	16	2·3	45	10	10	14	8	6	42·3
4	11	3·0	30	15	12	30	17	8	29·3
5	30	1·5	20	35	25	34	20	12	13·6
6	15	1·7	24	25	25	24	23	18	21·2
7	30	2·2	40	28	30	34	25	27	46·7
8	23	1·8	24	30	18	36	18	13	17·6
9	30	3·3	50	12	10	19	2	2	51·0
10	30	3·4	64	15	16	30	5	3	47·8

Conversion from Traditional Units to SI Units: 1mm Hg ≈ 0.133 kPa.

and a raised or normal left ventricular end-diastolic pressure.

The relation between the corrected PEP (PEPc) and corrected LVET (LVETc) in the two groups of patients is shown in Fig. 2. The PEPc in patients with cardiomyopathy was greater than 160 m/s and the LVETc less than 380 m/s, while the PEPc in patients with constrictive pericarditis was less than 160 m/s and the LVETc greater than 380 m/s. There was only a slight overlap between the two groups. The relation between the PEP/LVET ratio and the predicted EF is shown in Fig. 3. Again there is a clear discrimination between the two groups of patients. The PEP/LVET ratio of 0·5 and the EF of 0·5 are the dividing lines.

Statistical analysis of the haemodynamic findings (Figs. 4, 5, 6, and 7) shows highly significant differences between the two groups of patients.

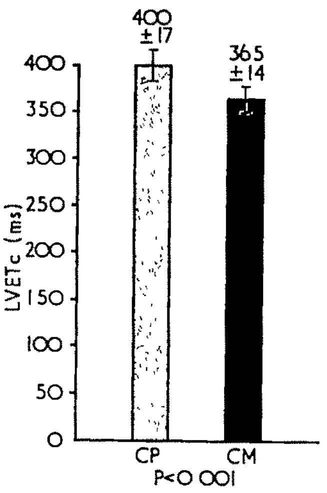

FIG. 5 *Statistical analysis of the results of LVETc in constrictive pericarditis and cardiomyopathy.*

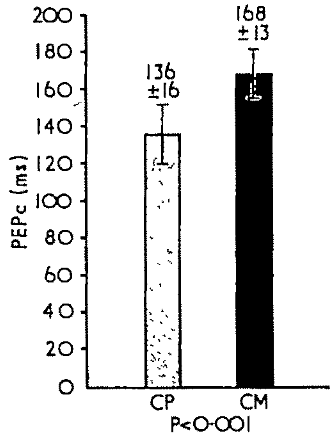

FIG. 4 *Statistical analysis of results of PEPc in constrictive pericarditis and cardiomyopathy.*

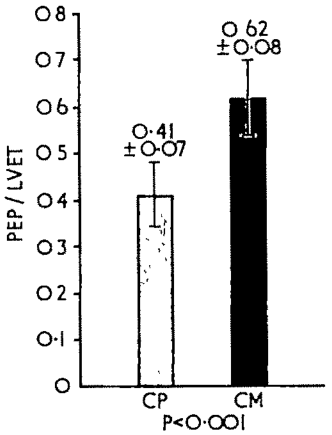

FIG. 6 *Statistical analysis of the results of PEP/LVET ratio in constrictive pericarditis and cardiomyopathy.*

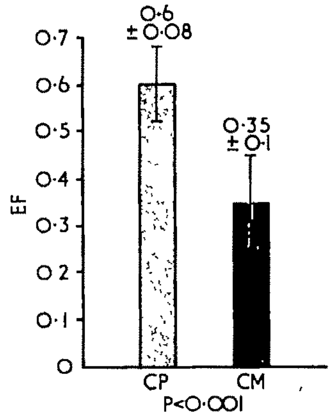

FIG. 7 *Statistical analysis of the results of EF in constrictive pericarditis and cardiomyopathy.*

Discussion

The systolic time intervals are a most effective and sensitive method of evaluating left ventricular performance. Alterations in the intervals—the increase in PEP and the decrease in LVET—closely correlate with other haemodynamic measurements of left ventricular dysfunction such as reduced cardiac output and stroke volume, decreased ejection fraction, and depressed left ventricular contractile performance as measured by peak left ventricular dP/dt (Weissler *et al.*, 1968, 1969; Garrard *et al.*, 1970; Ahmed *et al.*, 1972). In left ventricular dysfunction there is a decrease in the maximal rate of rise in isovolumetric pressure (Gleason and Braunwald, 1962) resulting in an increase in the time needed for the intraventricular pressure to reach the aortic diastolic pressure leading to prolongation of the pre-ejection period. When PEP is prolonged but the total electromechanical systole remains unchanged the left ventricular ejection time must decrease.

In cardiomyopathy there is gross myocardial dysfunction with decrease in myocardial contractility, as shown by left ventricular cineangiography and a low cardiac output and ejection fraction (Fowler, Gueron, and Rowlands, 1961; Yu *et al.*, 1964; Croxson and Raphael, 1969; Hamby *et al.*, 1970; Ghosh, Neelakantan, and Chhetri, 1974). The situation is, however, different in constrictive pericarditis, where the clinical picture of congestive heart failure is due to impaired ventricular filling with normal or near normal myocardial function (Armstrong, Lewis, and Gotsman, 1973; Gaasch, Peterson, and Shabetai, 1974). Thus the STI serve to differentiate between the two conditions (Armstrong *et al.*, 1973).

The STI clearly discriminated between the two groups of patients in our study. Significant abnormalities in STI were found in the cases of cardiomyopathy even when the patients were not in failure. PEP, LVET, PEP/LVET, and predicted EF differed between the two groups in nearly all cases, the most noticeable difference being in the PEP/LVET ratio and the EF. We therefore believe that systolic time intervals measured by simple, non-invasive bedside methods can differentiate between constrictive pericarditis and cardiomyopathy even when invasive procedures like cardiac catheterization and angiocardiography may fail.

We are grateful to the Surgeon Superintendent, S.S.K.M. Hospital, and the Director, Institute of Postgraduate Medical Education and Research, Calcutta, for their help and co-operation.

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Instantaneous mitral valve leaflet velocity and its relation to left ventricular wall movement in normal subjects

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Echocardiograms showing mitral valve leaflets, interventricular septum, and posterior wall of the left ventricle simultaneously were recorded at a paper speed of 100 mm/s in 20 normal subjects. These records were manually digitized and a computer was used to derive mitral valve velocity, left ventricular dimension, and its rate of change continuously throughout a single cardiac cycle.

The pattern of instantaneous mitral valve velocity with respect to time was similar in all subjects studied, showing a peak opening rate of 400 ± 60mm/s (mean ±1 SD), and continuously changing velocity throughout the period of mid-diastolic closure. The peak diastolic closure rate was 250 ± 60 mm/s and thus appreciably higher than average velocities obtained by manually measuring the slope.

A close time relation existed between mitral valve and left ventricular wall movement in early diastole. Forward movement of the anterior leaflet began 1 ± 6 ms after the onset of outward wall movement, and peak velocity was reached 2 ± 7 ms after the maximum rate of change of dimension. Later, a discontinuity in wall movement at the end of rapid filling preceded a corresponding discontinuity in the mitral valve velocity tracing by 5 ± 10 ms.

The technique, therefore, allows continuous measurement of mitral valve velocity, and demonstrates its close relation to left ventricular wall movement during diastole.

The diastolic closure rate of the anterior leaflet of the mitral valve is a fundamental measurement in echocardiography, and a number of disturbances of left ventricular function have been diagnosed on the basis of values lying outside the normal range (Feigenbaum, 1972). Initially, these measurements were made on the assumption that the velocity of valve movement was uniform throughout the period of mid-diastolic closure but more recently, biphasic (Quinones *et al.*, 1974; Madeira *et al.*, 1974) and intermediate (Rodger and Sumner, 1975) patterns have been described. In view of the physiological significance attributed to abnormalities of mitral valve movement and the diversity of means by which the measurements were made, we have modified traditional methods of study by recording echocardiograms at a paper speed of 100 mm/s and digitizing them manually to derive anterior leaflet velocity continuously throughout the cardiac cycle. This has permitted us to study the pattern of mitral valve movement in greater detail than was possible with previous methods and to compare its time relations with those of the left ventricular wall during ventricular filling.

Subjects and Methods

Subjects

Echocardiographic studies were performed on 20 normal volunteers in a resting state. Their ages ranged from 16 to 59, and 13 were men. All were in sinus rhythm and none had a previous history of heart disease.

Echocardiographic methods

All measurements were made with an Ekoline 20 ultrasonoscope (frequency 2·25 MHz, repetition frequency 1000/s). The output was displayed on a Cambridge multichannel strip chart recorder at a paper

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speed of 100 mm/s, with a simultaneous electrocardiogram. The subjects were studied in the supine or slightly left lateral position with the transducer at the left sternal border in the 3rd, 4th, or 5th interspace. The transducer was angled down from the aortic root through the mitral ring until echoes were obtained simultaneously from the septum, posterior wall, and the anterior leaflet of the mitral valve (Fig. 1). Measurements were only made on those recordings showing clear, continuous endocardial echoes from the septum and the posterior wall, and, in addition, the posterior mitral leaflet had to be recorded at least part of the time during diastole before the record was accepted for measurement.

Digitizing methods

Echocardiograms were digitized as previously described (Gibson and Brown, 1973), tracing echoes of the septum, posterior wall, anterior leaflet, and whenever possible, posterior leaflet, on a DMAC digitizing table interfaced with the IBM 1800 computer at Westminster Hospital. Strings of co-ordinates were generated for approximately 100 points on each of these echoes together with calibration signals representing 0·5 s, 1 cm, and the RR interval of the beat being studied.

Analysis of data

From the digitized data, plots were made of the positions of wall and leaflet echoes, instantaneous leaflet velocities, left ventricular dimension (D), rate of change of dimension (dD/dt), and normalized rate of change of dimension (1/D·dD/dt) (Fig. 2). Peak velocities of leaflet movement during early diastolic opening (D-E), mid-diastolic closure (E-F), atrial systolic opening (F-A), and end-diastolic closure (A-C) were measured directly. The times to peak opening and mid-diastolic closing velocities were measured directly and the corresponding accelerations derived as the mean slope of the velocity curve over the two intervals from the D and E points, respectively. In addition, the time relation between wall and mitral valve movement was analysed by measurement of the intervals between the time of 1) the onset of outward wall movement and that of the valve, 2) the peak rate of change of dimension and peak opening velocity of the valve, and 3) a discontinuity in the rate of wall movement and a corresponding one in the velocity tracing during mid-diastolic closure.

Critique of Methods

1) Measurement of position

All measurements of position of single echoes were made relative to the anterior chest wall. This does not affect estimates of left ventricular cavity size which was calculated as the distance between septal and posterior wall echoes and was thus independent of transducer position. Measurements of anterior leaflet velocity however, when made relative to any fixed external reference point, include a component caused by movement of the mitral ring (Zaky, Grabhorn, and Feigenbaum, 1967). In order to estimate the contribution of the latter, mitral ring echoes were recorded in 5 subjects and its velocity derived using the same methods as for the valve. Peak mitral ring velocities were small (less than 100 mm/s) and always occurred before those of the valve leaflets (Fig. 3). It appears, therefore, that measurement of the pattern of valve movement during diastole is not significantly distorted by use of the anterior chest wall as a reference point.

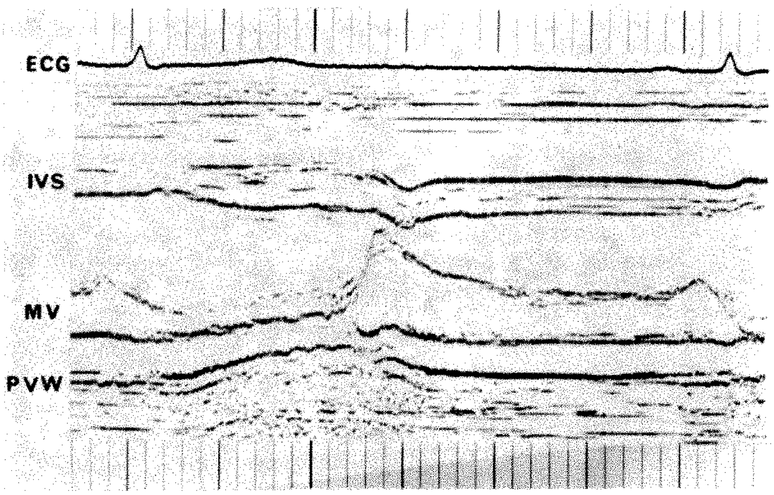

FIG. 1 *Echocardiogram recorded with a strip chart recorder at 100 mm/s showing interventricular septum (IVS), posterior left ventricular wall (PVW), and mitral valve (MV), with a simultaneous electrocardiogram (ECG).*

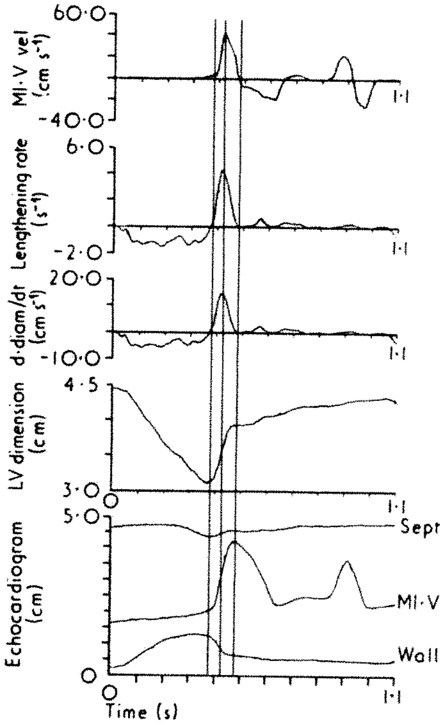

FIG. 2 *Computer output of digitized mitral valve and cavity echoes showing, from below, direct printout of echoes, left ventricular dimension, rate of change of dimension, normalized rate of change of dimension, and (top) instantaneous anterior mitral leaflet velocity. Vertical lines demonstrate: 1) onset of outward wall movement and anterior leaflet movement; 2) peak rate of wall and leaflet movement; and 3) discontinuity in wall movement and leaflet velocity during mid-diastolic closure.*

2) Technique of recording

Anterior mitral leaflet velocities were only measured from records which also showed echoes from the septum, the posterior wall, and at least part of the posterior leaflet. In order to compare measurements made in this position with those in which the ultrasound beam passed through the free edge of the leaflet, sweeps were made in 5 subjects of the mitral leaflet from the aortic root to its insertion into the papillary muscle. Derived velocities from successive beats were superimposed after being lined up on their respective QRS complexes (Fig. 4). It is apparent that estimates of peak velocity and the times to these peaks, vary little with position along the valve except that records derived from close to the aortic root show a pattern of movement intermediate between that of leaflet and ring.

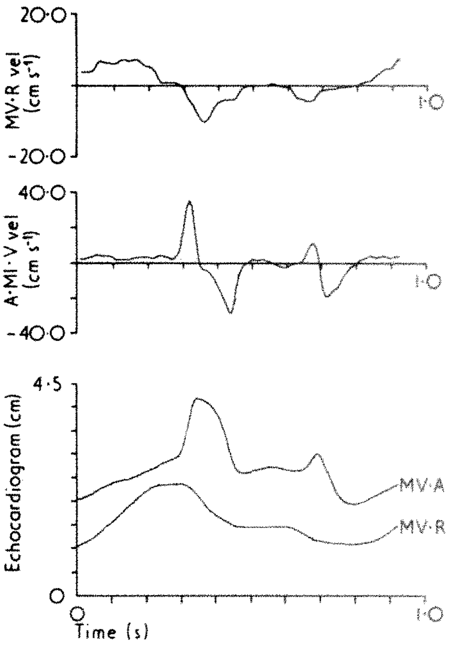

FIG. 3 *Computer output of digitized echoes from mitral valve and ring showing, from below, direct printout of echoes of ring (MVR) and anterior leaflet (MVA), instantaneous anterior leaflet velocity, and (top) instantaneous mitral ring velocity. Peak mitral ring velocity is less than leaflet velocity in diastole, and occurs earlier.*

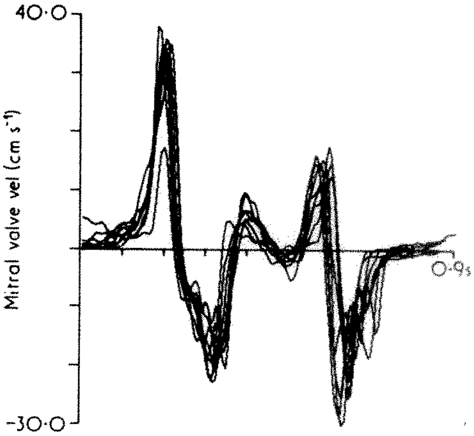

FIG. 4 *Eight superimposed velocity traces from the anterior leaflet in a single subject, obtained during a sweep from aortic root to mitral leaflet insertion into the papillary muscle.*

3) Relation of mitral leaflet movement to valve opening

In the present technique, the onset of forward movement of the anterior leaflet rather than actual valve opening is measured. Recent studies suggest that there is no direct relation between these two events and that valve opening may occur slightly later than the separation of the valve leaflets on the echocardiogram (Pohost *et al.,* 1975; Rubenstein *et al.,* 1975). Though the exact timing of mitral valve opening rather than the onset of forward movement of the anterior leaflet is not relevant to the present study, these observations are in line with angiographic data demonstrating outward wall movement before the appearance of unopacified blood from the left atrium within the left ventricular cavity (Prewitt *et al.,* 1975a).

4) Reproducibility

In 10 subjects, 2 successive beats were analysed by the same observer and reproducibility estimated as the root mean square difference between duplicate determinations. For paired velocities, these were 26 mm/s for early diastolic opening (D-E), 22 mm/s for mid-diastolic closure (E-F), 13 mm/s for atrial systolic opening (F-A), and 35 mm/s for end-diastolic closure (A-C); and for paired events of mitral valve and wall movement: 2·2 ms for the onset, 2·6 ms for the peak, and 3·7 ms for the discontinuity of movement.

5) Frequency response

The frequency response of the echocardiograph and digitizing system has previously been investigated in detail and found to be entirely adequate to study mitral valve and wall movement without distortion (Gibson and Brown, 1973).

Results

Mitral valve movement

A characteristic pattern of mitral valve movement was found in all 20 normal subjects studied (Fig. 5). After the onset of forward movement (D point), the velocity of the anterior leaflet increased until an early peak was reached and then returned rapidly to the baseline by the time of maximum excursion of the leaflet itself (E point). This same rapid rate of change of velocity persisted for a variable period during the early phase of mid-diastolic closure, but after an abrupt change in the slope of the curve, the rate of change increased more gradually until a late peak was reached. The curve then returned to the baseline by the time of maximum leaflet excursion in mid-diastole (F point). At no time was a constant velocity recorded during mid-diastolic closure, which would have resulted in one or more horizontal segments in the velocity tracing. Instead, early diastolic movement could be described in terms of four periods of nearly constant rate of change of velocity, i.e. of nearly constant acceleration. The first was from the onset of anterior movement of the leaflet to peak opening rate, the second from peak opening rate to the abrupt change in slope early during mid-diastolic closure, the third from this time until peak closure rate, and the fourth ending with the F point.

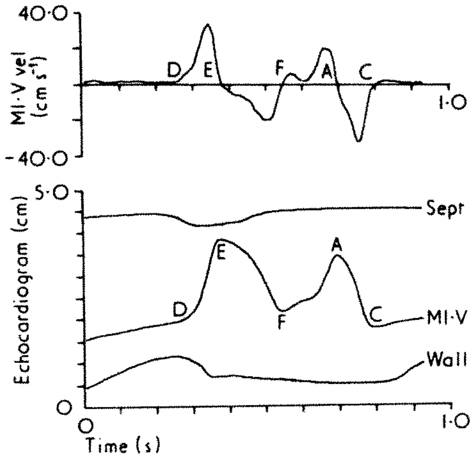

FIG. 5 *Computer output of digitized mitral valve echo (anterior leaflet), with its instantaneous velocity above.*

Similar deflections were found in the velocity tracing during atrial systolic opening and end-diastolic closure. The velocity curve of the posterior leaflet was virtually a mirror image of that of the anterior (Fig. 6).

Peak velocities

The mean value for the peak opening velocity of the anterior leaflet was 400 ± 60 mm/s and it occurred 60 ± 10 ms after the onset of forward movement (D point). The peak closing velocity was 250 ± 60 mm/s, occurring 100 ± 20 ms after the onset of mid-diastolic closure (E point). Thus, the mean slope during opening corresponded to an acceleration of 0·67 ± 0·15 g, and during mid-diastolic closure to an acceleration of −0·27 ± 0·08 g. The peak velocity during atrial systole was 250 ± 70 mm/s and during end-diastolic closure was 290 ± 80 mm/s.

In 5 patients in whom it was possible to record posterior leaflet velocities, the peaks were: 190 ± 40 mm/s for opening, 90 ± 10 mm/s for mid-diastolic closure, 110 ± 30 mm/s for atrial systolic opening, and 120 ± 40 mm/s for end-diastolic closure.

Relation of wall to mitral valve movement

In early diastole, there was a close time relation between left ventricular wall and anterior leaflet movement (Fig. 2). The onset of forward movement of the anterior leaflet followed that of outward wall movement by 1 ± 6 ms; the peak opening velocity followed peak rate of wall movement by 2 ± 7 ms, and later a discontinuity in the rate of wall movement preceded a similar discontinuity in mitral movement during mid-diastolic closure by 5 ± 10 ms. These corresponding events of wall and mitral valve movement were simultaneous as best we could determine, since the time intervals did not differ significantly from zero.

After the cusps separated, the posterior leaflet reached its peak opening velocity 20 ± 10 ms before that of the anterior leaflet, and the discontinuity during mid-diastolic closure also occurred 20 ± 10 ms earlier (Fig. 6).

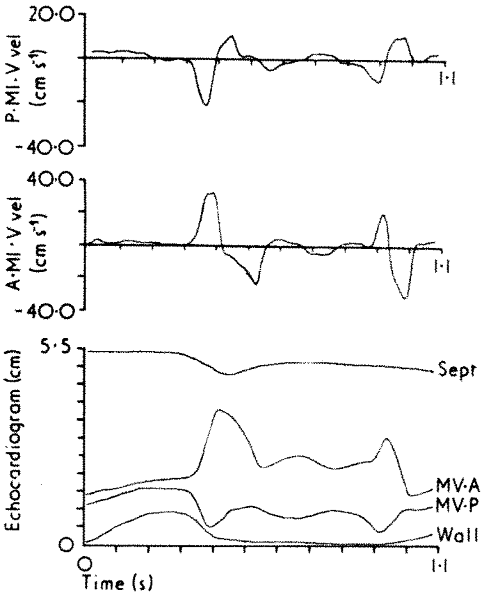

FIG. 6 *Computer output of anterior and posterior mitral leaflet echoes showing, from below, direct printout of echoes from posterior wall, posterior cusp (MVP), anterior cusp (MVA), and septum. Above are shown instantaneous velocities of anterior and (top) posterior cusps.*

Discussion

The rate of descent of the anterior mitral valve leaflet in mid-diastole was first noted to be diminished in mitral stenosis and the practice of measuring the diastolic closure rate was introduced to diagnose and quantify the severity of the disease (Edler, 1955; Effert, Erkens, and Grosse-Brokhoff, 1957; Gässler and Samlert, 1958). Since differences between normal and rheumatic valves were great, they could readily be demonstrated by simple manual measurements from records made at slow sweep speeds. It soon became apparent however, that the diastolic closure rate could be outside the normal range in the absence of mitral valve disease, and both increased (Segal, Likoff, and Kingsley, 1967; Madeira *et al.*, 1974) and decreased (Shah *et al.*, 1968; Popp and Harrison, 1969; Duchak, Chang, and Feigenbaum, 1972) values have been reported. In these circumstances, however, there is a spectrum of values from the normal to the abnormal range, and it has been suggested that this variable may be related in some way to ventricular filling or compliance (Zaky, Nasser, and Feigenbaum, 1968; Quinones *et al.*, 1974). Since these ideas have potential clinical significance, the need to determine diastolic closure rate unambiguously becomes apparent. These measurements are technically easy to make in mitral stenosis since the closure rate is constant throughout the greater part of diastole, but when the leaflet echo is normal, our results have shown that closure rate increases throughout the early diastolic filling period, so that the segment to be measured is curved. If a slow sweep speed is used to record the echogram, this curve is not apparent (Fig. 7) and manual estimation results in the mean rather than the peak value of the slope between the E and F points. If a faster sweep speed is used, then a tangent must be constructed whose slope is to some extent arbitrary. It is not surprising, therefore, that a wide range of values has been recorded for the normal diastolic closure rate, diminishing the specificity of this variable (Table). It is unlikely that this scatter is caused by any differences in the populations of normal subjects studied but rather it seems to reflect lack of uniformity in methods of recording and analysing the echocardiograms.

In order to resolve these difficulties, we have recorded mitral valve echograms at a fast paper speed using a strip chart recorder and have used a digitizing technique to derive velocity continuously throughout the cardiac cycle. Measurements of diastolic closure rate made in this way cannot be compared directly with others already published,

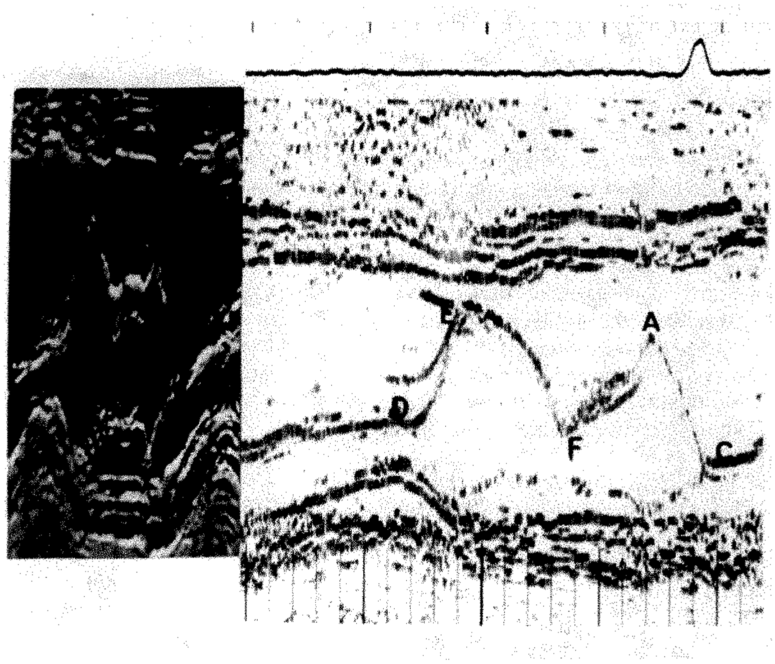

FIG. 7 *Echograms of the mitral valve recorded in the same subject on Polaroid film (left) and a strip chart recorder at 100 mm/s (right). It is apparent from the record on the right that the velocity of closure is not constant during mid-diastole but this is not obvious on the record on the left, taken at a lower sweep speed.*

since we have derived peak rather than mean values, so that the figure of 250 ± 60 mm/s for that of the anterior leaflet is considerably higher than previously reported in normal subjects (Table).

TABLE *Values reported for the normal diastolic closure rate*

Study	*Year*	*Range (and mean) (mm/s)*
Edler and Gustafson	1957	85–150 (120)
Effert	1959	86–200 (125)
Joyner, Reid, and Bond	1963	85–160
Segal *et al.*	1967	70–150
Winters *et al.*	1969	65–210
Popp and Harrison	1969	80–150
Pridie, Benham, and Oakley	1971	70–120
Ross	1972	70–160 (114)
Layton *et al.*	1973	58–139 (92)
Quinones *et al.*	1974	60–110 (85)
Madeira *et al.*	1974	115–225 (173)
Rodger and Sumner	1975	128–234 (176)

Measurements of posterior leaflet velocity were also made and shown to be approximately half the corresponding values for the anterior leaflet, with a peak diastolic closure rate of 90 ± 10 mm/s. The mitral ring contributed little to mitral valve movement during diastole, since its peak velocity was considerably lower and occurred earlier than that of either anterior or posterior leaflet.

The use of continuous digitization also allowed the pattern of mitral valve movement to be investigated. The form was similar in all normal subjects and showed a series of periods of relatively constant acceleration, resulting in continuously changing velocity. The time intervals over which these accelerations appeared to operate were not necessarily synchronous with valve position. For example, the rapid deceleration at the end of early diastolic opening of the leaflets frequently persisted beyond the time of maximum opening and so caused a brief rapid acceleration at the onset of mid-diastolic closure.

Since the normal mitral leaflets are thin and pliable, acceleration and deceleration of blood into the ventricle seems to provide the force necessary for mitral valve movement. This idea is not new since in 1837, Mcartney *et al.* suggested that mid-diastolic closure might occur, and 6 years later, Baumgarten (1843) clearly showed this event in association with deceleration of flow into the isolated left ventricle. More recently, the presence of vortices behind the valve leaflets has been demonstrated experimentally (Henderson and Johnson, 1912; Brockman, 1966; Bellhouse, 1972) while Laniado *et al.* (1975) in dogs have shown close correlation between transmitral blood flow and valve movement. Our results are compatible with these observations. The virtually simultaneous onset of mitral valve and outward wall movement and the close relation between the two during early diastole suggest that the forces acting on the valve are closely related to the pattern of ventricular filling. If valve movement is assumed to obey simple Newtonian mechanics, the application of a constant force would result in a period of constant acceleration. Our results suggest that during early diastole, valve movement can be described in such terms, with the initial three periods of acceleration each apparently corresponding to a well-defined phase of ventricular filling. The first phase of acceleration terminates with peak opening rate which is synchronous with the peak rate of wall movement and therefore with the 'O' point of the apex cardiogram (Prewitt *et al.*, 1975b) and the nadir of the ventricular pressure trace (Willems, de Geest, and Kesteloot, 1971). This initial period of filling, when ventricular volume increases as pressure is still falling, is one which departs widely from any simple passive model (Dodge, Hay, and Sandler, 1962). The second period of valve movement extends from peak opening rate to the discontinuity on the velocity trace during mid-diastolic closure. This occurs at the same time as a corresponding discontinuity on the dimension record, noted as long ago as 1910 by Straub and more recently shown to correspond, in many cases, with the third heart sound (Prewitt *et al.*, 1975b). Finally, the period of lesser acceleration which terminates with peak closure rate is associated with a greatly reduced rate of outward wall movement. The fourth period, ending when the leaflet reaches the closed position, does not correspond to any feature of wall movement, so that the constraint on the valve may be the result of some other factor such as a restraining force developed by the subvalve apparatus.

In contrast to early diastolic events, atrial systolic opening and presystolic closure were not accompanied by significant wall movement. The reason for this is not clear from our observations but may have been the result either of a different mechanism of valve closure during atrial systole, or of failure of changes in left ventricular diameter to reflect filling in late diastole. In favour of the latter explanation are the observations of Laniado *et al.* (1975) in the dog, who demonstrated atrial systolic opening to be accompanied by a significant increase in transmitral flow. Further evidence in man comes from lower estimates of left ventricular volume changes during atrial systole made by echocardiography (Gibson and Brown, 1973) in comparison with those derived from angiocardiograms (Hammermeister and Warbasse, 1974), while the asymmetrical pattern of left ventricular filling at this stage of the cardiac cycle can be demonstrated angiographically, the increased volume being accommodated almost exclusively by prolongation of the long axis (Gibson and Brown, unpublished).

If the pattern of mitral valve movement is to be used as an index of ventricular filling in early diastole, it seems likely that continuous measurement of instantaneous velocity rather than estimation of mean values will reflect the rapidly changing determinants of blood flow into the left ventricle during this period. There is some evidence that comparison of mitral valve and wall movement may have practical significance since the close relation between the two provides an additional criterion of normality. Preliminary results suggest that this close relation may be lost when ventricular contraction is impaired and the normal filling pattern of the left ventricle disturbed (Upton, Gibson, and Brown, 1975).

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Left ventricular angiography on exercise

A new method of assessing left ventricular function in ischaemic heart disease

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Left ventricular function was studied in 17 patients with ischaemic heart disease and compared with 4 patients with normal left ventricular function. The patients in the homogeneous group of ischaemic heart disease were further subdivided into those 'without angina' (n=5) and those 'with angina' (n=12), depending upon the presence of angina during supine leg exercise at the time of definitive study. At rest there was no significant difference in the heart rate, cardiac output, stroke volume, and left ventricular end-diastolic pressure (LVEDP) in the three groups. During exercise the cardiac output and stroke volume were significantly depressed and LVEDP was significantly raised in the ischaemic heart disease group as a whole but within this group failed to show any significant difference in patients with and without angina. The left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) measurements showed clear separation of these three groups only on exercise. On exercise, there was decrease in LVEDV and LVESV ($P < 0{\cdot}05$; $P < 0{\cdot}02$) in the group with normal left ventricular function, no change in the group with ischaemic heart disease without angina, and striking increase in LVEDV and LVESV in the group with ischaemic heart disease and angina ($P < 0{\cdot}01$ and $P < 0{\cdot}02$, respectively). This angiographic method of assessing left ventricular function shows clear separation of the three groups and also highlights the significance of angina. Ejection fraction (EF), a commonly measured parameter of left ventricular function, failed to reflect consistent changes on exercise as compared to values at rest which emphasizes the limitations of the measurement of ejection fraction at rest.

Coronary artery bypass surgery in patients with ischaemic heart disease is expected to prevent myocardial ischaemia and to increase or restore coronary blood flow to the underperfused areas, thereby improving left ventricular function. But there are many reports indicating that the improvement in ventricular function studied at rest has not been shown to be consistent with the symptomatic relief achieved by the surgical treatment (Achuff *et al.*, 1972; Miller *et al.*, 1972; Bourassa *et al.*, 1972; Shepherd *et al.*, 1974). Probably one of the main reasons is that left ventricular function in coronary artery disease at rest is often within the normal range and, therefore, does not allow an accurate definition of the functional reserve (Roskamm *et al.*, 1970). Hence, evaluation of left ventricular function in patients with ischaemic heart disease under stress is important. The following study was designed to assess ventricular function and pressure/volume changes during the physiological stress of exercise in patients with ischaemic heart disease who were being investigated for consideration of coronary artery bypass surgery.

Subjects and methods

Patients

Seventeen male patients with ischaemic heart disease were studied for consideration of coronary artery bypass graft surgery. The average age of the group was 41 years (range 29 to 60), average weight 76 kg (range 67 to 82), and average surface area was 1·74 m² (range 1·64 to 1·93). The average length of the history of angina was 5 years (range 1 to 12); none had valvular heart disease, hyper-

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tension, or diabetes. A reliable and definitive history of myocardial infarction was present in 8 patients; none had present or past evidence of heart failure. At the time of study, on clinical examination, a third heart sound was present in 1, and a fourth heart sound was audible in 6 patients. The resting 12-lead electrocardiogram was normal in 9 patients; definitive evidence of old myocardial infarction was present in 7 patients (pathological Q wave and ST-T changes); non-specific ST-T changes were present in the praecordial leads in 1 patient; definitive evidence of anterolateral infarction was found in 5, inferior infarction in 1, and combined anterior and inferior infarction in 1 patient. During treadmill exercise, angina was provoked in all, associated with horizontal or downward sloping ST segment depression of 1 mm or more in lead V5. This ST depression induced by exercise, rapidly reverted back to the pre-exercise level with complete resolution of chest pain during recovery period. The chest radiograph was normal and the cardiothoracic ratio was less than 50 per cent in all. None had received any drug other than nitroglycerin for 2 days before the study.

Four male patients, referred for suspected heart disease, were also included. None was found to have any haemodynamic or electrocardiographic abnormality either at rest or during exercise. All had normal coronary and left ventricular angiograms; none had mitral or aortic valve lesions. Thus, all were considered to have normal left ventricular function. The average age of these patients was 40 years (range 28 to 52), average weight 75 kg (range 62 to 81), and average surface area 1·78 m^2 (range 1·70 to 2·05). Thus, the patients with ischaemic heart disease and normal left ventricular function were homogeneous in age, sex, weight, and body surface area.

The haemodynamic investigations were an essential part of the diagnostic procedure in each patient. The purpose of the extension of the diagnostic investigations by exercise left ventriculography was explained to each patient. The procedures involved were demonstrated during a rehearsal session and their possible significance in the understanding and treatment of angina were specifically discussed with each patient. The voluntary nature of their co-operation was emphasized without inducement (Medical Research Council Report, 1964; Ormrod, 1968).

Design of investigation

Before the definitive study, patients were familiarized with the investigative techniques and, at the same time, trained to do supine leg exercise. A bicycle ergometer was used in 11 patients and the remaining 10 patients were trained to raise their legs alternately, approximately 12 times a minute against adjustable weights suspended on pulleys. Exercise was equal and submaximal in all and judged by measuring oxygen uptake during the final 2 minutes in 11 patients. The predetermined level of exercise enabled us to predict the onset of angina in the definitive study. The normal left ventricular function group underwent a similar programme.

On the day of the study, selective coronary arteriography was performed first. Haemodynamic measurements at rest were followed by left ventriculography. Fifteen to twenty minutes were allowed to elapse for the return of circulatory changes to the pre-angiography level. Patients were then exercised at the predetermined level until the onset of angina, or for a total period of six minutes. Haemodynamic measurements were repeated during the final 2 minutes of exercise and left ventriculography was repeated immediately after exercise: no time was allowed to elapse between the conclusion of exercise and the injection of contrast medium into the left ventricle as the patients continued exercise during positioning for angiography in the right anterior oblique position. Cardiac output was measured in 11 patients by the Fick method during the rest period and during the final 2 minutes of exercise. At the end of the study, glyceryl trinitrate was given sublingually to all those patients who developed angina during exercise.

Haemodynamic methods

Blood samples for arteriovenous oxygen differences were collected from pulmonary and brachial arteries through small nylon catheters introduced percutaneously into the brachial artery and via the median antecubital vein for the pulmonary artery. An additional nylon catheter (75 × 0·1 cm) was introduced into the left ventricle percutaneously via the brachial artery for simultaneous and continuous measurement of the left ventricular pressure during angiography in 11 patients. In the remaining 10 patients the left ventricular pressures were recorded by multilumen angiographic catheter (Ducor, Cordis, 8F). Pressures were measured by Stratham P32 strain gauge transducers. The manometers were calibrated over the range 0 to 80 and 0 to 20 mmHg (0 to 10·6 kPa and 0 to 2 7 kPa) for the measurement of left ventricular systolic and left ventricular end-diastolic pressures, respectively, which was arranged to span 10 cm on the recording paper; over this scale the manometers were linear within 2 per cent; the maximum undamped natural frequency of the nylon catheter in the left ventricular pressure measurement was found to be 60 Hz, with damping ratio 0·5. The natural frequency of the multilumen 'pigtail' angiographic catheter was found to be 30 Hz, with damping ratio of 0·25. From high frequency recording of left ventricular pressures in dogs, Gersh, Hahn, and Prys-Roberts (1971) demonstrated that the first six harmonics of Fourier analysis contain sufficient data for measurement of systolic and diastolic pressure to be made with ±5 per cent. At a heart rate of 90 to 120 faithful reproduction of sixth harmonics is achieved with catheter manometer systems response of 9 to 12 Hz. Using such methods under similar conditions of study, duplicate measurement of cardiac output, left ventricular end-diastolic pressure agreed to within 5 and 8 per cent, respectively, of the mean value both at rest and during exercise. The electrocardiogram was recorded with a disc adhesive electrode from chest lead V5 and calibrated externally (0·1 mV = 1 mm). The intravascular pressures and electrocardiogram were continuously monitored on the oscilloscope and recorded at minute intervals on a multichannel recorder.

Angiographic method

Left ventriculography was performed through a multilumen angiographic catheter (Ducor, Cordis, 8F) inserted percutaneously into the femoral artery and retrogradely positioned into the left ventricle under radiological screening control. The radio-opaque contrast media (76% Urografin) was infused by electromechanical pump (Contrac, Contraves, Zurich) at a rate of 10 ml/s for 5 seconds at rest and 15 ml/s for 5 seconds for the exercise left ventriculography. Simultaneous biplane cineangiograms were recorded in 11 patients; single-plane right anterior oblique angiograms in the remaining 10 patients. The patient held his breath in inspiration during filming. Left ventriculograms were studied for abnormal left ventricular contraction by viewing; details of this method of assessing dykinesia are given elsewhere (Sharma *et al.*, 1975b).

The measurement of left ventricular volumes was made at end-diastole and end-systole. During biplane filming simultaneous frames were identified by electronic integration. Biplane filming was at a speed of 75 frames per second and single-plane recordings were made at a speed of 48 frames per second, both on 35 mm films. The values for volume measurements represent the average mean of the first three beats during angiography.

Simultaneous measurement of left ventricular pressures and volumes were made in 11 patients. In the rest of the 10 patients, left ventricular pressures in the first 5 beats immediately before angiography were analysed. Left ventricular volumes were calculated by the semi-area-length method by assuming that the left ventricular chamber can be represented as an ellipse (Kasser and Kennedy, 1969). The films were projected on a Vanguard analyser onto a screen. Chamber length and area were determined by a cursor connected to an Olivetti 602 programmable calculator which transferred the area measurements by Simpson integration into volume measurement automatically. The magnification factors were predetermined for film and heart height combination; analysis showed that there was insignificant pin cushion distortion (J. Darman, 1974, personal communication). The left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were identified in each beat by volume time curve. Further angiographic calculations were:

$$\text{Stroke volume (SV)} = \text{LVEDV} - \text{LVESV}$$

$$\text{Ejection fraction per cent (EF)} = \frac{\text{SV}}{\text{LVEDV}} \times 100$$

$$\text{Cardiac output (CO)} = \text{SV} \times \text{heart rate}$$

The LVEDP was measured at the nadir of the atrial wave just before the systolic contraction in the left ventricular pressure curve. Electrocardiographic ST depression in chest lead V5 was measured from the J point to the isoelectric line joining two consecutive PR intervals.

Measurement, calculations, and statistical analysis

Statistical analyses were based on the orthodox methods; within the group probability of statistical significance of difference was calculated by the t-test for paired data; significance of difference between the groups relates to the comparison of means (unpaired t-test).

Results

Of 17 patients with ischaemic heart disease, 12 developed chest pain associated with ischaemic ST depression. The average time of onset of pain was 285 ±20 seconds (range 180 to 360) and average ST depression was 2·4 ±0·4 mm (range 0·1 to 3·6). These patients were subgrouped as *ischaemic heart disease with angina.* The other 5 patients with ischaemic heart disease developed neither angina nor ST depression during exercise at the time of the study and were subgrouped as *ischaemic heart disease without angina.* The four patients in the normal left ventricular function group had neither angina nor ST depression during similar exercise.

Selective coronary angiography

In the normal left ventricular function group, the coronary arteriograms were normal in all; there were no obstructive significant lesions in the right and left coronary arteries. In patients with ischaemic heart disease, significant lesions (>50% obstruction) of the left anterior descending artery were found in 7 patients, and of the right coronary artery in 1 patient; two-vessel disease of left anterior descending and right coronary artery in 2 patients; left anterior descending and left circumflex in 2 patients, and left circumflex and right coronary artery in 2 patients. Three-vessel disease was found in one patient. The coronary artery lesions were comparable in both subgroups of ischaemic heart disease, with or without angina at the time of definitive study.

Effects of left ventriculography (Table 1)

Left ventriculography at rest and immediately after exercise was carried out without any complication in all patients. In 11 patients, haemodynamic measurements were made before, during, and 2 minutes after the injection of radio-opaque contrast medium. There was no significant change in the heart rate and left ventricular peak systolic (LVSP) and end-diastolic pressure measured just before and during ventriculography, either at rest or during exercise. But 2 minutes after angiography at rest there was a significance increase in

TABLE 1 *Haemodynamic effects of left ventriculography (11 patients)*

Variable	*Rest*			*Exercise*		
	Preangio[1]	*During angio*[2]	*Post-angio*[3]	*Preangio*[1]	*During angio*[2]	*Post-angio*[3]
Heart rate/min	75±3	76±3	80±5	124±8	124±8	125±9
LV Peak systolic pressure (mmHg)	144±8	143±8	137±7 *	185±15	179±10	167±12 **
LV end-diastolic pressure (mmHg)	8±1	10±2	18±2 ***	32±4	29±3	34±4

Significance in difference relates to the preangio measurements at rest and during exercise: *P <0·05; **P <0 03; ***P <0·01.

[1] Average mean of first 5 beats just before injection of radio-opaque contrast media into the left ventricle.

[2] Average mean of first 3 beats during injection.

[3] Average mean of 5 beats after 2 minutes of angiography.

Conversion factor from Traditional to SI units: 1 mmHg ≈ 0·133 kPa.

LVEDP (P <0·01) and a decrease in LVSP (P <0·05). During left ventriculography on exercise there was no significant change in the heart rate or LVEDP, but LVSP was significantly lower (P <0·02) as compared to the preangiographic values. These results indicate that radio-opaque contrast medium during the first three beats produces insignificant haemodynamic change. Thus, preangiographic haemodynamic measurement can be taken to represent haemodynamic changes during angiography. Therefore, in the remainder of the 10 patients it was decided not to measure simultaneous pressures with angiography because it required two catheters in the left ventricle. Volumetric analysis during the first three beats has been regarded as true left ventricular volume devoid of any effect of the contrast medium (Carleton, 1971). By contrast the left ventricular dysfunction produced by contrast medium 2 minutes after injection in patients with ischaemic heart disease is in agreement with the findings of Rahimtoola, Gau, and Raphael (1970).

Reliability of volumetric analysis

The biplane method of measuring left ventricular volume is an established method for the quantitative assessment of left ventricular function (Dodge *et al.*, 1966; Dodge and Baxley, 1969; Arvidsson, 1961; Kennedy *et al.*, 1968). In this study left ventricular volumes were estimated by biplane technique in 11 patients (in 4 normals and 7 patients with ischaemic heart disease) and single plane technique in 10 patients. In clinical practice, single plane right anterior oblique cineangiography is more commonly employed for assessment of myocardial function and localization of abnormal left ventricular contraction in patients with ischaemic heart disease. Good correlation exists between single plane and biplane angiographic measurements (Sandler *et al.*, 1965; Sandler and Dodge, 1968; Herman and Bartle, 1968). Cardiac output measured at rest and during exercise by the angiographic method correlated well with cardiac output measured by the Fick method in 11 patients (correlation coefficient = 0·922; Fig. 1). The cardiac outputs of 10 patients were derived from the volume measurements which have been shown to be extremely reliable (Dodge, Hay, and Sandler, 1962). The

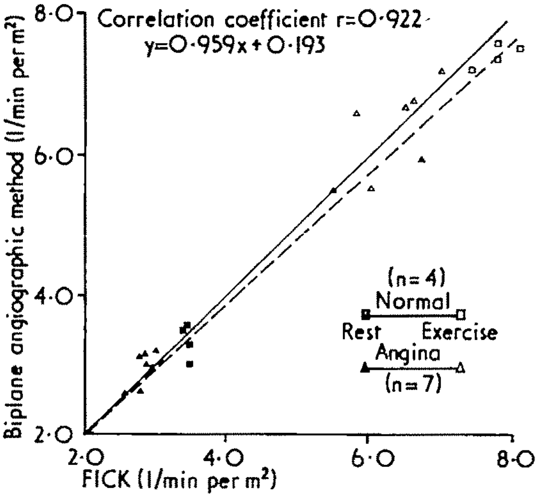

FIG. 1 *Shows good correlation between direct Fick and biplane angiographic method of measuring cardiac output; dotted line—x=y; solid line—regression line.*

TABLE 2 *Haemodynamic, angiographic, and electrocardiographic data*

Variable	*Normal left ventricle (n=4)*		*Ischaemic heart disease (n=17)*			
			Without angina (n=5)		*Angina (n=12)*	
	Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
Heart rate/min	68±1·5	112±3 *****	70±4	118±8 *****	71±1	110±4 *****
Cardiac output (angio.) (l/min per m² BSA)	3 3±0·1	7·8±0·2 *****	3·1±0·1	6·3±0·4 ***	2·9±0 1	6·6±0·3 ***
Stroke volume (angio.) (ml/beat per m² BSA)	51±0·6	68±1·7 ****	45±2	54±4 **	43±2	60±2 ***
LV peak systolic pressure (mmHg)	136±5	175±8 ***	140±5	185±9 ***	138±5	186±8 ***
LV end-diastolic pressure (mmHg)	8±1	14±5 ***	12±2	25±3 **	13±1	34±3 ****
LV end-diastolic volume (ml per m²)	78±3	70±1 *	80±3	84±4	97±2	139±3 ****
LV end-systolic volume (ml per m²)	27±3	6±2 ***	34±4	30±3	46±3	76±4 ***
Ejection fraction (%)	63±4	92±4 **	58±3	66±3	54±2	46±2 *
S T depression (V5) (mm)	0·0±0·0	0 2±0·2	0·0±0·0	0·5±0·4	0·6±0·4	2·4±0·4 **

Data expressed as mean ± SEM; Significance of difference between rest and exercise within the same group:
*P <0·05; **P <0·03; ***P <0·02; ****P <0·01; *****P <0·001. *Conversion factor from Traditional to SI units:*
1 mm Hg ≈ 0·133 kPa.

duplicate error by 2 independent observers in the measurement of left ventricular volume was ±4·2 ml (n = 42).

Haemodynamic changes (Tables 2 and 3; Fig. 2)

At rest, there was no significant difference in the heart rate, cardiac output, stroke volume, LVEDP, and the LVSP when compared in the 3 groups. Though there was no significant difference in the average values of resting LVEDP in patients with ischaemic heart disease as compared with normal subjects, data from individual patients revealed that only 4 had an LVEDP higher than 15 mm Hg (2·0 kPa) at rest.

During exercise, the average oxygen uptake was 645 ±11 ml/min per m² BSA; heart rate and LVSP were similar in all 3 groups. The cardiac output and stroke volume were depressed in the ischaemic heart disease group as a whole, but within this group there was no statistically significant difference in patients with and without angina. Similarly, LVEDP during exercise rose significantly to higher levels in all patients with ischaemic heart disease (P <0·03) as compared to the patients in the normal left ventricular function group, but within the ischaemic heart disease group the rise in LVEDP showed no statistically significant difference in patients with and without angina.

Thus, haemodynamic values at rest in patients with ischaemic heart disease were in no way any different from those with normal left ventricular function. It was only exercise that separated patients with ischaemic heart disease from normal subjects.

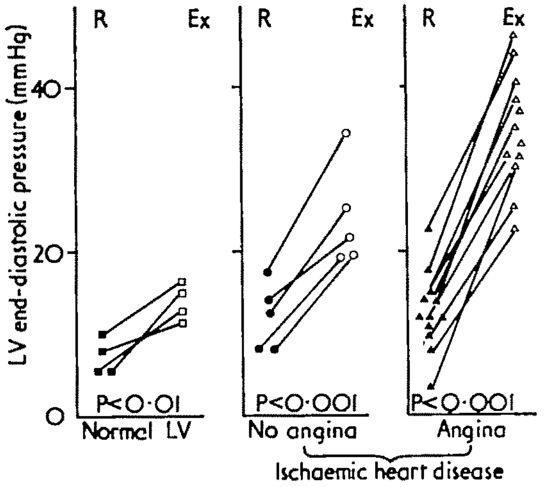

FIG. 2 *LVEDP during exercise is raised significantly in all patients with ischaemic heart disease. There is no significant difference in LVEDP in patients with ischaemic heart disease with and without angina; R—rest; Ex—exercise; P value related to the significance between rest and exercise.*

TABLE 3 *Statistical analysis between groups*

Variable	*Normal ventricle group* vs. *Ischaemic heart disease without angina*		*Normal left ventricle* vs. *Ischaemic heart disease with angina*		*Ischaemic heart disease without angina* vs. *Ischaemic heart disease with angina*	
	Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
Heart rate/min	NS	NS	NS	NS	NS	NS
Cardiac output (angio.) (l/min per m²)	NS	< 0·03	NS	< 0·03	NS	NS
Stroke volume (ml/beat per m²)	NS	< 0·05	NS	< 0·05	NS	NS
LV end-diastolic pressure (mmHg)	NS	< 0·05	NS	< 0·02	NS	NS
LV end-diastolic volume (ml per m²)	NS	< 0·03	NS	< 0·001	NS	< 0·01
LV end-systolic volume (ml per m²)	NS	< 0·02	NS	< 0·001	NS	< 0·01
LV peak systolic pressure (mmHg)	NS	NS	NS	NS	NS	NS
Ejection fraction (%)	NS	< 0·02	NS	< 0·001	NS	< 0·05
ST depression (mm)	NS	NS	NS	< 0·01	NS	< 0·03

NS = Statistically not significant.

Left ventricular dyskinesia

Localized diminished, absent, or paradoxical areas of myocardial contraction of the left ventricle, as observed from the angiogram, were defined as 'dyskinesia'. At rest and during exercise none of the patients with normal left ventricular function showed dyskinesia. In the ischaemic heart disease with angina group, 6 had dyskinesia at rest; in these the area of dyskinesia was further extended during exercise. The remaining 6 patients with normal left ventricular contraction at rest developed new areas of dyskinesia during exercise. The details of these findings and their implications have been discussed elsewhere (Sharma *et al.*, 1975b).

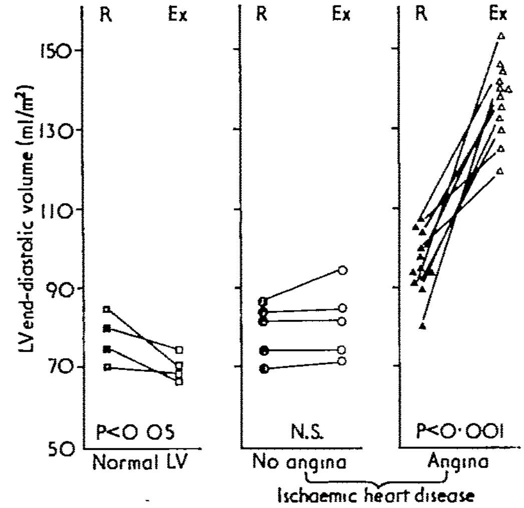

FIG. 3 *Effect of submaximal exercise on LVEDV. During exercise LVEDV falls in normal subjects, remains the same in ischaemic heart disease without angina, and increases considerably in ischaemic heart disease with angina; NS=not significant.*

Left ventricular volume changes (Fig. 3 to 6; Tables 2 and 3)

Left ventricular end-diastolic volume (LVEDV)

At rest the LVEDV was within normal range in all three groups. The LVEDV in ischaemic

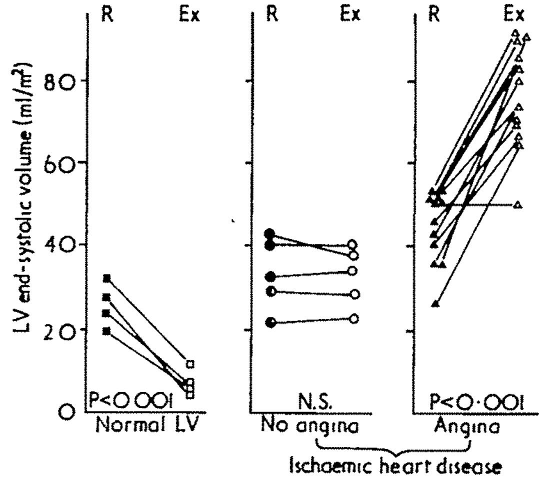

FIG. 4 *Effect of submaximal exercise on LVESV. During exercise LVESV decreases in normal subjects, remains the same at rest in ischaemic heart disease without angina, and increases in ischaemic heart disease with angina.*

heart disease with angina tended to be higher than in the other groups, but because of wide scatter this difference did not reach statistical significance. During exercise there was a 10 per cent decrease in LVEDV in the normal left ventricular function group ($P < 0{\cdot}05$), no significant change in the ischaemic heart disease group without angina, and a 43 per cent increase in the ischaemic heart disease group with angina ($P < 0{\cdot}01$), all being compared to the values at rest. Between the groups during exercise the LVEDV was higher in the ischaemic heart disease without angina ($P < 0{\cdot}03$) and ischaemic heart disease with angina ($P < 0{\cdot}001$) compared to the group with normal left ventricular function, showing clear separation of the 3 groups.

Left ventricular end-systolic volume (LVESV)

All 3 groups showed normal ranges of LVESV at rest. Though the values of LVESV tended to be higher in patients with ischaemic heart disease with angina, the differences were not statistically significant. During exercise LVESV decreased in the group with normal left ventricular function ($P < 0{\cdot}02$), did not change in the ischaemic heart disease group without angina, and showed a significant increase in ischaemic heart disease with angina ($P < 0{\cdot}02$) indicating insufficient emptying of the left ventricle in patients with ischaemic heart disease. There was a statistically significant difference in LVESV during exercise in the group with normal left ventricular function, those with ischaemic heart disease without angina, and those with ischaemic heart disease with angina when these groups were compared with each other.

Ejection fraction

This is the conventional angiographic method of assessing left ventricular function. Ejection fraction did not differ significantly at rest in all three groups. Though the average mean was lower in patients with ischaemic heart disease with angina, it failed to reach statistically significant difference. During exercise the group with normal left ventricular function increased their ejection fraction significantly as compared to the values at rest ($P < 0{\cdot}03$) and also when compared with other groups (ischaemic heart disease without angina, $P < 0{\cdot}02$; ischaemic heart disease with angina, $P < 0{\cdot}001$); within the ischaemic heart disease group, patients with angina had lower ejection fractions at rest than patients without angina ($P < 0{\cdot}05$).

Ejection fraction failed to reflect consistent changes during exercise in the patients with ischaemic heart disease with angina. In this group some patients having an ejection fraction less than 50 per cent, indicating poor left ventricular function at rest, were found to increase ejection fraction above 50 per cent. On the other hand, the majority of the patients in this group had an ejection fraction greater than 50 per cent and decreased their ejection fraction during exercise. All patients with new or extended areas of dyskinesia and angina were found to have a significantly depressed ejection fraction ($P < 0{\cdot}05$).

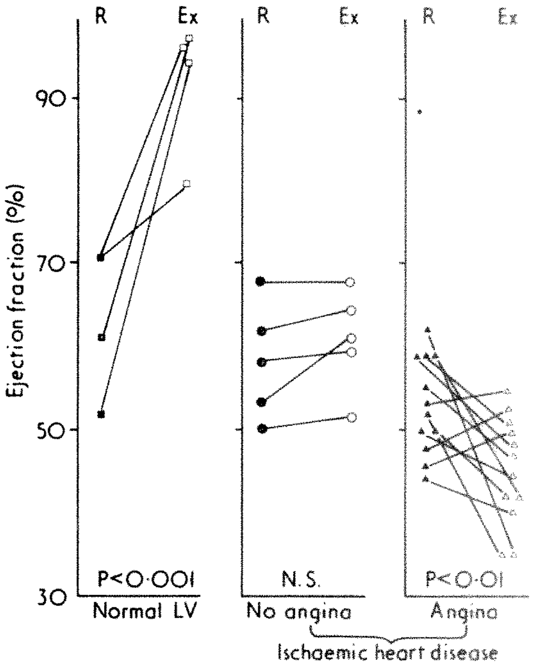

FIG. 5 *Effect of submaximal exercise on ejection fraction. This study shows that ejection fraction at rest does not predict the state of left ventricular function during exercise.*

Assessment of left ventricular function

The ejection fraction and LVEDV in the clinical situation represent the indirect evidence of myocardial fibre shortening and initial diastolic fibre length, respectively (Hamilton, Murray and Kennedy, 1972). A left ventricular function curve has been constructed by plotting ejection fraction against LVEDV (Fig. 7). Data in patients with normal left ventricular function showed good function during exercise with increase in ejection fraction and decrease in LVEDV. In patients with ischaemic heart disease with angina, the increase in LVEDV was associated with a decrease in ejection fraction, but patients with ischaemic heart disease without angina showed a flat response (no change in either LVEDV or ejection) during exercise. On the basis of left ventricular function these 3 groups have shown clear separation only on exercise.

In order to assess the relation between systolic and diastolic volume of the left ventricle, LVESV was plotted against LVEDV. These volumes represent the end results of systole and diastole, respectively (Fig. 8). These findings indicate that in patients with ischaemic heart disease, there is proportionate systolic and diastolic dysfunction of the left ventricle.

Discussion

This study has confirmed that in ischaemic heart disease in the absence of myocardial ischaemia at rest, ventricular function can remain within the normal range; exercise has been shown to unmask the impairment of the left ventricular function as evidenced by the presence of abnormally raised LVEDP, depressed stroke volume, and cardiac output. When exercise was accompanied by angina, cardiac output, LVEDP, and stroke volume did not change any further, but there were statistically significant increases in ventricular volumes as

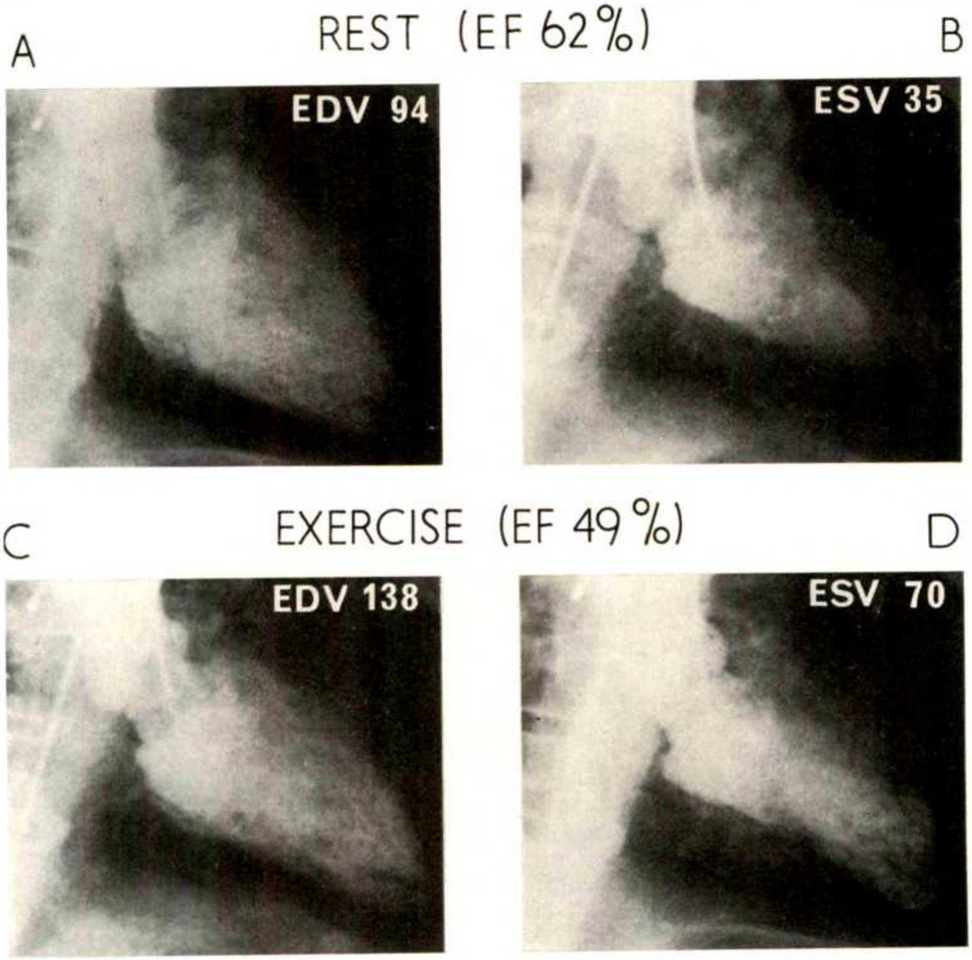

FIG. 6 *Left ventricular cineangiograms performed at rest and during myocardial ischaemia (angina and ST depression 2·1 mm in lead V5) induced by exercise in a patient (J.S.; 48 years) with a 5-year history of ischaemic heart disease, who was assessed for coronary artery bypass surgery. This patient shows ventricular dilatation, incomplete left ventricular emptying, and fall in ejection fraction during angina induced by exercise. ED, ES and EF represent end-diastole, end-systole, and ejection fraction, respectively (see text).*

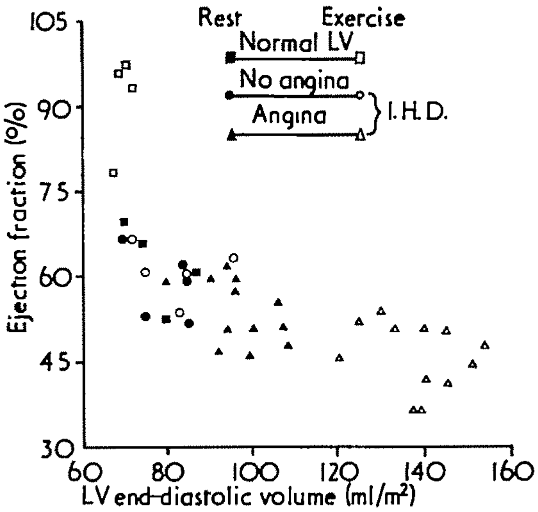

FIG. 7 *Comparison of the left ventricular function by plotting LVEDV and ejection fraction as indices of diastolic fibre length and systolic fibre shortening, respectively. The results in normal left ventricular function* (top left), *ischaemic heart disease without angina* (middle), *and ischaemic heart disease with angina* (bottom right corner of the diagram), *show clear separation of these groups during exercise, indicating good function in normal left ventricle group and poor left ventricular function in the ischaemic heart disease with angina group.*

measured angiographically. These changes clearly separated the patients with angina on effort from those without angina and the normal left ventricular group. Thus, certain haemodynamic and angiocardiographic investigations during exercise were proved to be of value in assessing the functional cardiac reserve and significance of angina.

In normal subjects, supine exercise causes an increase in sympathetic tone and thus a rise in the heart rate and contractility, which together with the decrease in peripheral resistance and simultaneous increase in venous return (Topham and Warner, 1967) results in an increase in cardiac output and stroke volume, corresponding to the demand of the periphery (Ross *et al.*, 1966). The present study has shown similar changes in cardiac output, stroke volume, and heart rate measurements, confirming these observations. In normal subjects the values of volumetric analysis (LVESV, LVEDV, and ejection fraction) at rest are in agreement with others (Kennedy *et al.*, 1966; Miller and Swan, 1964; Sanmarco and Bartle, 1964). During supine submaximal exercise there was a small decrease in LVEDV, a striking decrease in LVESV, and, consequently a significant increase in ejection fraction. A similar physiological response to exercise has been reported by others (Rushmer, Smith, and Franklin, 1959; Holmgren and Ovenfors, 1960). Harrison, Goldblatt, and Braunwald (1963) observed decrease in the left ventricular dimensions by an average of 13 per cent during supine submaximal leg exercise.

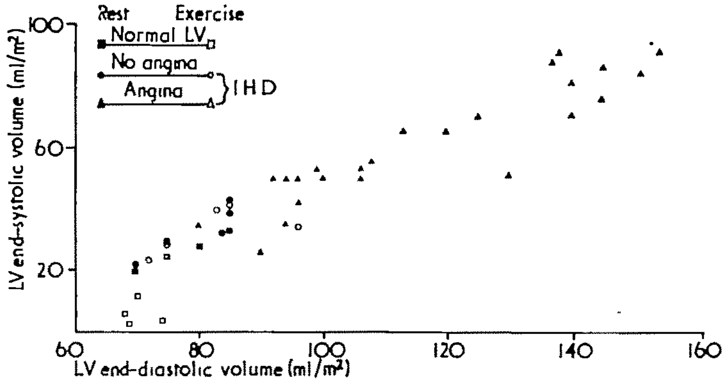

FIG. 8 *Correlation between LVEDV and LVESV shows no disproportionate impairment in these two measurements at rest and during exercise.*

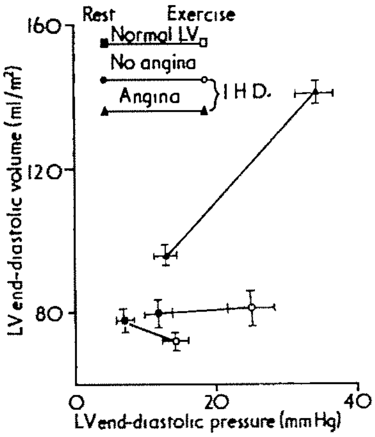

FIG. 9 *Pressure-volume relation at rest and during exercise. This study indicates left ventricular dilatation during exercise-induced angina.*

In patients with ischaemic heart disease the haemodynamic and angiographic measurements at rest were not significantly different from normal subjects, which indicates that assessment of left ventricular function at rest alone may be of only limited value for the management of such patients. During exercise, the patients with ischaemic heart disease have been shown to respond differently. The conventional methods of assessing the resting function of the heart (cardiac output, stroke volume, and LVEDP) do separate patients with ischaemic heart disease from those with normal function but fails to separate ischaemic patients with and without angina of effort. The deterioration in left ventricular function, shown by volume measurement on effort, clearly separates the angina group from the group without angina.

Though exercise in patients with ischaemic heart disease is associated with abnormally raised LVEDP and the symptoms of angina (Müller and Rørvik, 1958; Wiener, Dwyer, and Cox, 1968; Sharma and Taylor, 1970), the precise significance of LVEDP to the onset of exercise-induced angina is far from clear. It is apparent in this study, and shown by others (Lichtlen, Baumann, and Albert, 1969), that LVEDP can be raised during exercise irrespective of angina in patients with ischaemic heart disease. Before the onset of pain, the LVEDP frequently rises far earlier during the course of exercise and reaches a plateau, thus bearing no relation to angina (Lichtlen, 1971). Furthermore, when LVEDP, one of the haemodynamic determinants of myocardial oxygen consumption, was either altered or controlled as discretely as possible with the help of right atrial pacing, propranolol, phentolamine, and ouabain, and the effects of these changes were observed on the onset and total duration of angina, there was no consistent relation between the LVEDP and angina (Sharma, Majid, and Taylor, 1975a). On the other hand, exercise left ventriculography and data on the ventricular volumes in this study have defined the significance of angina. The presence of angina was associated with an area of abnormal left ventricular contraction (dyskinesia) related to major obstructions of the corresponding coronary artery (Sharma and Taylor, 1975); these dyskinetic segments were not present in either the normal left ventricular function group or patients with ischaemic heart disease without angina (Sharma *et al.*, 1975b). Also in the presence of angina of effort there were large increases in LVESV and LVEDV. Eubanks *et al.* (1970) have also shown similar changes in the ventricular volume during exercise-induced pain in patients with ischaemic heart disease. There is also suggestive evidence that the magnitude of changes in LVEDV may play a role in both the production and amelioration of pain in patients with angina pectoris (Parker *et al.*, 1970).

The question whether raised LVEDP during pain in patients with ischaemic heart disease is associated mainly with loss of compliance or largely reflects ventricular dilatation, remains debatable. This study supports the view that angina induced by exercise is accompanied by ventricular dilatation (Fig. 9), hence left ventricular failure, which is also supported by another study (Eubanks *et al.*, 1970). The concept of loss of compliance emerges from the studies carried out by atrial pacing (Dwyer, 1970; Barry *et al.*, 1974). Though atrial pacing is a safe and useful technique for producing angina and ST depression (Sowton *et al.*, 1967), it is by no means physiological, for atrial pacing causes abrupt shortening of diastole and prevents adequate and complete relaxation of the ventricle. Experimental evidence in dogs suggests that encroachment upon the diastolic period results in incomplete relaxation which in turn leads to changes in diastolic compliance (Monroe and French, 1961; Mitchell, Linden, and Sarnoff, 1960; Templeton, Ecker, and Mitchell, 1972) so that results obtained by atrial pacing are difficult to interpret in physiological terms.

Traditionally, LVEDP is a widely used haemodynamic measurement for the evaluation of the left ventricular function in clinical practice and therefore deserves further comment in relation to ischaemic heart disease. The decision to carry out revascularization surgery in ischaemic heart disease often depends on the LVEDP, yet there is a lack of positive correlation between LVEDP and postoperative results (Johnson and Lepley, 1970; Chatterjee *et al.*, 1971). Furthermore, LVEDP has not been shown to be an absolute index of left ventricular function (Chatterjee *et al.*, 1971), and the present study has distinctly revealed that LVEDP may not necessarily reflect changes in LVEDV (Fig. 9). The LVEDP should be regarded as a poor substitute for LVEDV (a measure of diastolic fibre length) in constructing Frank Starling's ventricular function curve in man.

Another widely accepted measure of left ventricular function is the ejection fraction (EF). Ejection fraction of 50 per cent or more is regarded as a normal ventricular response at rest. The limitation of ejection fraction at rest is clearly shown in this study (Fig. 5). Ejection fraction measured at rest does not predict the response to exercise in patients with ischaemic heart disease. In the group of patients with ischaemic heart disease and angina the majority of patients with an ejection fraction of 50 per cent or more at rest have decreased their ejection fraction during exercise and vice versa; this further highlights the limited value of the measurements at rest.

Experimental evidence suggests that a definite relation exists between end-diastolic and end-systolic volume in a given set of circumstances (Tyberg *et al.*, 1970). During an enhanced contractile state of the heart the decreased end-diastolic volume and decreased vascular impedance to ejection induces smaller end-systolic volumes (Tyberg *et al.*, 1970). Similarly the physiological response to exercise in man is characterized by reduced end-diastolic volume and increased ejection fraction (Rushmer *et al.*, 1959), all of which result in a decrease in end-systolic ventricular volume. The present study has shown a close relation between LVEDV and LVESV in patients with ischaemic heart disease and normal left ventricular function at rest as well as during exercise (Fig. 8). There was no dissociation between systolic and diastolic impairment of left ventricular function as judged by LVESV and LVEDV. This relation may be explained on the concept of an equilibrium volume (volume at zero pressure) as elucidated by Brecher, Kolder, and Horres (1966) under set animal experimental conditions. Small LVESV (less than equilibrium volume) is more likely to be achieved by a small LVEDV and vice versa. Though the present study was not designed to elucidate this fact and none of the variables was controlled, it clearly shows that a relation between LVEDV and LVESV exists in normal subjects as well as patients with ischaemic heart disease during variable inotropic state of the heart.

Left ventricular volume analysis by angiographic methods has been shown to provide useful information in coronary artery disease with wide varieties of ventricular dysfunction present at rest (Hamilton *et al.*, 1972), but its usefulness during exercise has been clearly demonstrated in this study. Thus, volume measurements should not be regarded purely as an academic exercise for assessing the inotropic and contractile state of the myocardium but they have valuable uses in determining the surgical and medical management of patients with ischaemic heart disease.

The results of this study point quite clearly to the limitations of the assessment of left ventricular function at rest and the value of studying the heart on exercise in order to evaluate improvement of the functional cardiac reserve after coronary artery bypass surgery. It is our intention to restudy these patients after successful coronary artery bypass graft at the level of exercise similar to those obtained before operation, to determine if surgery improves left ventricular function.

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Clinical experience with left main coronary artery stenosis

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We report the clinical features and the results of investigation and surgery in 20 patients with significant left main coronary artery stenosis. All had moderate to severe angina; 8 had pain at rest. Three had dyspnoea as a major symptom.

The electrocardiogram was abnormal in 17, with evidence of previous myocardial infarction in 10. Of the 11 patients exercised, 8 developed chest pain. Nine patients had a normal left ventriculogram.

At coronary angiography all patients had major disease elsewhere in addition to the left main coronary artery stenosis. There were no deaths or major complications associated with this investigation.

One patient was unsuitable for surgery because of diffuse left ventricular hypokinesia, one had a fatal myocardial infarction while awaiting operation, and there was one peroperative death. Sixteen of the 17 surgical survivors are free from angina. There has been a significant improvement in the maximum exercise capacity in the 10 patients who had pre- and postoperative exercise tests.

Stenosis of the main stem of the left coronary artery carries a poor prognosis, with less than half the medically treated patients surviving 5 years after diagnosis (Bruschke, Proudfit, and Sones, 1973; Webster, Moberg, and Rincon, 1974; Cohen *et al.*, 1972). The earlier reports on investigation and surgery in patients with this lesion suggest that both are associated with a high mortality (Cohen *et al.*, 1972; Lavine *et al.*, 1972).

In the four-year period, November 1970 to October 1974, we investigated angiographically 665 patients with suspected coronary artery disease. Twenty of these had stenosis of the left main coronary artery of more than 75 per cent. The clinical features and the results of investigations and surgery in this group are reported.

Methods

The investigation protocol followed has been reported previously (Balcon *et al.*. 1974). Angina and dyspnoea were graded from 1 to 4, using the same criteria as the New York Heart Association grading for dyspnoea. Routine chest radiographs and electrocardiograms were made. The electrocardiographic diagnosis and localization of myocardial infarction were based on the criteria of McConahay *et al.* (1970). The patients had fasting serum cholesterol and triglyceride estimations and lipoprotein electrophoresis, and the lipoprotein abnormality was typed using the World Health Organization classification (1970). Patients performed a standardized exercise test in the upright position on a bicycle ergometer with electrocardiographic recording from a bipolar chest lead. Exercise started at 150 kpm/min (24·5 Watts) and increased by 150 kpm/min (24·5 Watts) every two minutes until the development of angina, ST segment depression of 2 mm or more, dyspnoea, or fatigue.

Left heart catheterization was performed from the right brachial artery after premedication with intramuscular diazepam. The resting left ventricular end-diastolic pressure was recorded and those without chest pain at rest were paced, usually from the right atrium, until the patient developed angina. Left ventriculograms were graded from 0 to 4, 0 being normal and 1 to 4 showing an increasing area of abnormal movement. Coronary angiography was performed by the Sones technique in all cases. The angiographic severity of coronary artery disease was represented by a numerical score. Each major vessel was scored on a scale of 0 to 4; 0 was normal, 4 total occlusion, and 1 to 3 stenosis of increasing severity (1 less than 50%, 2 50 to 75%, and 3 75 to 99%).

Operation was usually performed within four weeks of investigation but patients with recurring episodes of rest

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TABLE 1

			Angina						*Serum lipids*				*Beta-adrenergic blocking agents*	
Case no.	*Age (yr)*	*Sex*	*Grade*	*Duration (mth)*	*Dyspnoea*	*Previous myocardial infarction*	*Electrocardiogram*	*Chest radiograph*	*Cholesterol (mg/dl)*	*Triglycerides (mg/dl)*	*Lipoprotein abnormality*	*Trinitrin*	*Agent*	*Dose/day (mg)*
1	49	M	3	60	—	+	AMI and IMI	Normal				+	Propranolol	240
2	48	M	4	3	—	0	Normal	Normal	360	288	Type2b	0	—	—
3	42	M	2	3	1	+	IMI	Normal	240	230	Type 4	0	—	—
4	63	M	2	6	3	0	IMI	Cor+PVC	245	278	Type 4	0	—	—
5	59	M	4	8	—	0	Transient ST depression	Normal	200	285	Type 4	+	Practolol	300
6	59	M	3	96	3	+	IMI	Enlarged heart, PVC	225	207	Type 4	+	—	—
7	45	M	3	72	—	0	LBBB	Normal				+	Propranolol	240
8	51	M	3	120	—	+	IMI	Normal	175	384	Type 4	0	Practolol	200
9	51	F	2	6	1	0	ASMI	Normal	356	133	Type2a	0	Propranolol	60
10	60	M	4	36	—	0	Transient ST depression	Normal	260			+	Propranolol	120
11	48	M	2	12	2	0	Normal	Normal	286	220	Type 4	+	Practolol	300
12	49	M	2	60	—	+	ASMI	Normal				0	Propranolol	120
13	52	M	4	72	—	+	AMI	Normal	164			+	Oxprenolol	120
14	34	F	4	3	—	0	Transient ST depression	Normal	242	85	Normal	+	—	—
15	47	M	3	108	—	+	Inverted T in V3–6	Normal	260	24	Normal	+	Practolol	800
16	68	M	2	6	3	+	IMI	Enlarged heart, PVC	265	150	Normal	0	—	—
17	50	M	4	132	2	+	AMI and IMI	Enlarged heart				+	Oxprenolol	120
18	66	M	4	120	—	0	Transient ST depression	Normal	275			+	—	—
19	49	M	2	36	1	0	Normal	Normal	190	150	Normal	0	—	—
20	40	M	4	12	1	0	Inverted T in V3–6	Normal	235	180	Normal	+	Practolol	200

AMI, anterior myocardial infarction; IMI, inferior myocardial infarction; LBBB, left bundle-branch block; ASMI, anteroseptal myocardial infarction; PVC, pulmonary venous congestion. *Conversion from Traditional to SI units:* Cholesterol: 1 mg/dl≃0·02586 mmol/l; triglyceride: 1 mg/dl≃0·0113 mmol/l.

pain had operation within 24 hours of coronary angiography. These latter patients had continuous electrocardiographic monitoring and regular sublingual trinitrin to relieve chest pain in the interval between angiography and surgery, but in no case was it considered necessary to use balloon counterpulsation.

Great care was taken to avoid any fall in blood pressure during induction of anaesthesia, and where necessary pressor agents were used. In all cases the heart was prepared for bypass as quickly as possible. Once on bypass the major division of the left coronary artery was prepared and an anastomosis, using either the left internal mammary artery or a long saphenous vein, was carried out. Occasionally an endarterectomy was performed first. If a vein was used it was immediately anastomosed to the aorta to establish coronary flow as quickly as possible. The other diseased arteries were grafted as necessary. Normothermic bypass was used throughout, together with elective fibrillation and aortic cross-clamping for periods up to 15 minutes as required.

The patients were seen at three months, six months, and then yearly after operation. Exercise tests were performed at each visit.

Results

The clinical data are shown in Table 1. There were 18 men and two women with ages ranging from 34 to 68 years (average of 52 years). Angina was the main symptom in 17, but was also present in the 3 other patients whose main complaint was dyspnoea. The mean grade of angina was 3·1 out of 4 (range 2 to 4). Eight patients had episodes of pain at rest. The mean duration of angina was 48 months, but was less than 6 months in 6 patients. Nine patients had a history of previous myocardial infarction. Four had diabetes (Cases 3, 4, 8, and 11). The mean serum cholesterol concentration was 249 mg/dl (6·4 mmol/l) with a range from 164 to 360 mg/dl (4·2 to 9·3 mmol/l). Six patients had a type 4 lipoprotein abnormality, one a type 2a and one a type 2b. The resting electrocardiogram was abnormal in 17, with 10 patients showing changes consistent with previous myocardial infarction.

Four had transient ST segment depression during

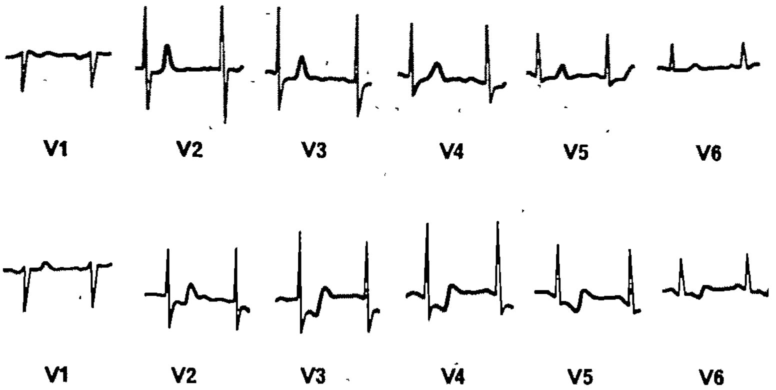

FIG. 1 *Transient ST depression occurring at rest during angina.*

TABLE 2

Case no.	*Duration of follow-up (mth)*	*Angina grade*		*Maximum exercise load and end-point (kpm/min)*	
		Preoperative	*Postoperative*	*Preoperative*	*Postoperative*
1	21	3	0	600, angina	1050, fatigue
2	14	4	0	600, ST depression and angina	750, fatigue and dyspnoea
3	12	2	1	600, dyspnoea	750, fatigue and dyspnoea
4	9	2	0	Not done	450, fatigue
5†	—	4	—	600, ST depression and fatigue	Died awaiting operation
6	6	3	0	150, dyspnoea and fatigue	300, fatigue
7	7	3	0	Not done	600, fatigue
8	9	3	0	450, dyspnoea	750, dyspnoea
9	10	2	0	450, angina	600, fatigue and dyspnoea
10	35	4	0	Rest pain	600, dyspnoea and ST depression
11	24	2	0	600, angina	750, fatigue
12	18	2	0	450, angina	600, fatigue
13	19	4	0	Not done	600, fatigue
14†	—	4	—	Rest pain	Died at operation
15	18	3	0	300, ST depression and angina	600, dyspnoea, fatigue and ST depression
16	4	2	Non-surgical		
17	4	4	0	600, angina	600, fatigue
18	3	4	0	Rest pain	Not done
19	3	2	0	Not done	1050, fatigue
20	3	4	0	Rest pain	900, fatigue

†Hospital death. 1 kpm/min=0·1635 Watt

episodes of rest pain. Fig. 1 shows intermittent ST depression at rest in Case 18. Four patients had cardiomegaly on chest *x*-ray. Twelve had been treated with sublingual trinitrin and 12 with beta-adrenergic blocking agents.

Eleven patients performed the exercise test before operation (Table 2). The mean maximum exercise level achieved was 490 kpm/min (80·1 Watts) with a range of 150 (24·5 Watts) to 600 kpm/min (98·1 Watts). The end-point in eight of these was angina and in three it was dyspnoea. Three of the patients who were limited by angina developed ST depression of 2 mm or more at end-point.

Cardiac catheterization data are shown in Table 3. Eleven patients underwent the pacing stress test during catheterization. Angina was induced in these at heart rates ranging from 100 to 170 beats per minute. Five other patients had angina at rest during catheterization. The resting left ventricular end-diastolic pressures ranged from 5 to 48 mmHg (0·7 to 6·4 kPa), with a mean of 16 mmHg (2·1 kPa).

The left ventriculogram was normal in 9 patients. Five had a grade 1, 3 a grade 2, and 2 a grade 3 abnormality on their ventriculogram. Only 1 patient had diffuse left ventricular dysfunction (grade 4).

TABLE 3

			Coronary arteries: grading of disease †			
Case no.	*Left ventricular end diastolic pressure (mmHg)*	*Maximum pacing rate (beats/min) at angina*	*Left anterior descending*	*Left circumflex*	*Right*	*Left ventricular angiographic grade*
1	17	150	2^{m}	3*	1	1
2	5	170	2*	4*	0	0
3	17	150	3*	3*	3*	1
4	12	Rest pain	2*	3	4*	2
5	16	100	3	0	1	0
6	25	Not done	3*	1	4*	3
7	25	Not done	2*	2*	3* E	1
8	7	150	4* E	2	4* E	0
9	15	150	3*	3*	3*	1
10	48	Rest pain	0*	0*	3	2
11	7	110	3*	3*	2	0
12	10	170	4*	0*	2	2
13	10	130	3*	3	3	0
14	18	Rest pain	1*	3*	2	0
15	10	150	3^{m}	3*	4*	1
16	18	Not done	3	4	4	4
17	26	150	D* 4*	3	4*	3
18	8	Rest pain	2	2*	3*	0
19	12	Not done	3*	3*	0	0
20	20	Rest pain	D* 3*	3*	2*	0

Conversion from traditional to SI units: 1 mm Hg≈0·133 kPa

†All patients had grade 3 stenosis of left main coronary artery

m, vessel bypassed with left internal mammary artery

*, vessel bypassed with saphenous vein

E, endarterectomy

D, diagonal branch left anterior descending grafted

All had at least one other major lesion (grade 3 or 4) in the coronary tree besides the left main coronary artery stenosis. Six patients had lesions of 2 other vessels and a further 6 had lesions of 3 vessels. The right coronary artery was affected in 12. There was radiographic calcification in the region of the left main stem in only 3 patients (Cases 1, 16, and 19). There were no major complications associated with the investigation.

One patient (Case 5) had a fatal myocardial infarction in hospital while awaiting operation. Another patient (Case 16) who presented with dyspnoea was considered unsuitable for surgery, because of diffuse left ventricular hypokinesia.

Eighteen patients had surgical treatment. The vessels bypassed and the types of graft used are indicated in Table 3. One patient had a single graft, 11 had double, 5 had triple, and 1 quadruple grafts. A prior endarterectomy was performed on 3 vessels and the left internal mammary artery was used twice. The graft flow was measured in 24 vessels and ranged from 30 to 140 ml/min, with a mean of 78 ml/min.

One patient (Case 14) became hypotensive during induction of anaesthesia and developed resistant ventricular fibrillation. At thoracotomy a large portion of the left ventricle in the region supplied by the left coronary artery was non-contractile. A double coronary artery graft was performed but the patient did not survive operation.

The follow-up data are shown in Table 2. The mean duration of follow-up is 12·2 months. There have been no late deaths or myocardial infarctions. Only one patient (Case 3) of the 17 surgical survivors has angina. Sixteen patients have had postoperative exercise tests. The mean maximum level achieved after operation was 684 kpm/min (111·8 Watts), with a range of 300 to 1050 kpm/min (49 to 171·7 Watts). In Fig. 2 a comparison of the mean preoperative with the latest postoperative exercise level achieved by 10 patients indicates a significant improvement in performance. The 6 patients who did not have a preoperative exercise test have a mean postoperative exercise performance of 700 kpm/min (114·5 Watts).

Discussion

The incidence of left main coronary artery stenosis among patients investigated for coronary artery disease in our department is 3 per cent. Wolfson, Grant, and Ross (1973), who also reported on left

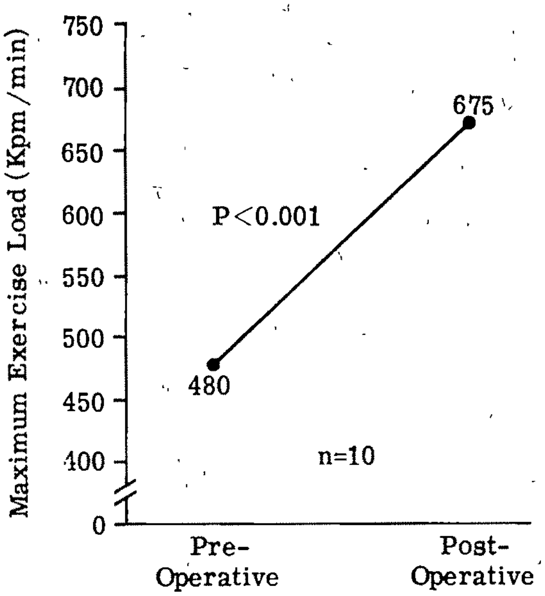

FIG. 2 *The results of pre- and post-operative exercise tests.*

main coronary artery stenoses of 75 per cent or greater, found a similar incidence. Other authors (Cohen *et al.*, 1972; Khaja *et al.*, 1974; Proudfit, Shirey, and Sones, 1967) who reported on stenoses of more than 50 per cent found an overall incidence varying from 2·5 to 5·9 per cent.

The majority of our patients had severe angina. Cohen *et al.* (1972) while recognizing that there were no features specific to left main coronary artery stenosis, suggested it could be anticipated before angiography in patients showing a 'profound ischaemic response' on their electrocardiogram during exercise. 82 per cent of their group and 77 per cent of Khaja's group had a positive exercise test. Only 27 per cent of our group who exercised on a bicycle ergometer developed ST depression. This discrepancy may be related to the method of exercise testing used, or to the fact that we recorded from a single praecordial lead.

Major coronary lesions other than left main coronary artery stenosis were present in all our patients. This is the usual finding both at coronary angiography (Lavine *et al.*, 1972; Rosch *et al.*, 1973) and at necropsy (Bulkley and Roberts, 1974). Lavine *et al.* (1972) in their report comment that the clinical features of these patients may be as much a reflection of the generalized coronary artery disease as of the left main coronary artery lesion.

The risk of coronary angiography in these patients is well known (Cohen *et al.*, 1972; Lavine *et al.*, 1972). Some authors (Cohen *et al.*, 1972; Rosch *et al.*, 1973) have suggested a preliminary test injection in the left posterior sinus of Valsalva in patients with suspected left main coronary artery disease. As indicated above, however, we were seldom able to predict from clinical findings, exercise testing, or other parameters, those patients likely to have left main coronary artery stenosis. Nevertheless, there were no major complications and no fatalities associated with angiography in this series, nor in other recently reported series (Khaja *et al.*, 1974; Zeft *et al.*, 1974).

Surgical mortality for left main coronary artery stenosis from the reported series ranges from 8·2 to 39 per cent (Pichard *et al.*, 1973; Zeft *et al.*, 1974; Khaja *et al.*, 1974; Cohen *et al.*, 1972; Kisslo *et al.*, 1973). The surgical mortality for our group (5·5 per cent) lies between our overall figures of 1·9 per cent for patients with effort angina and 12·5 per cent for patients with cardiac pain at rest. Hypotension during induction of anaesthesia is a recognized hazard in these patients (Cohen *et al.*, 1972). The surgical death in our group was related to this complication, though precautions had been taken to avoid it. The striking symptomatic improvement among the surgically treated group has been mirrored in their improved exercise performance.

Our studies have led us to the conclusion that patients with left main coronary artery stenosis also have severe coronary lesions elsewhere but behave no differently from other patients with severe coronary artery disease, either from the clinical and investigative point of view, or in their distinct symptomatic improvement with surgical treatment.

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Sustained release procainamide in patients with myocardial infarction

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Sustained release procainamide tablets were administered to 34 patients 48 hours after the onset of an acute myocardial infarct. Therapeutic blood levels of procainamide in the range of 4 to 8 μg/ml were consistently achieved using an 8-hourly maintenance dose of 1·5g after an initial loading dose of 2g. In contrast conventional procainamide capsules administered to 21 comparable patients repeatedly failed to produce plasma concentrations in the therapeutic range, despite the administration of a maintenance dose of 375 mg 3 hourly, after a loading dose of 1g. It is suggested that when the oral administration of procainamide is indicated for the management of ventricular arrhythmias after myocardial infarction, a sustained release preparation should be used.

In the acute phase after myocardial infarction, ventricular arrhythmias are a common cause of death. They also occur in the weeks and months after infarction (Norris *et al.*, 1968; Lawrie, 1969; Sloman *et al.*, 1970). The management of such patients is initially with intravenous lignocaine, but subsequent management over a period of days or weeks requires an oral antiarrhythmic drug. Procainamide is a potent antiarrhythmic agent which is active against both ventricular and supraventricular arrhythmias. Oral procainamide has been reported to provide effective prophylaxis against ventricular arrhythmias during the acute phase of infarction (Koch-Weser *et al.*, 1969). The absorption of procainamide is normally complete within two hours and elimination is predominantly by renal glomerular filtration and tubular excretion (Koch-Weser, 1971) though a small amount is metabolized to N-acetyl procainamide (Dreyfuss *et al.*, 1972). Elimination is rapid and the biological half-life averages 3·5 hours. The therapeutic range is between 4 and 8 μg/ml (Koch-Weser and Klein, 1971), though other workers (Giardina, Heissenbuttel, and Bigger, 1973) have suggested that 10 μg/ml can be approached without toxicity. In order to maintain plasma procainamide levels within this therapeutic range, the importance of a 3-hourly dosage regimen has been stressed (Koch-Weser *et al.*, 1969). Recently Shaw and coworkers (1974) have evaluated a 4-hourly dosage regimen using 375 to 500 mg and noted that it was unsatisfactory in maintaining effective plasma levels in 36 per cent of patients even at the highest dose. The inconvenience of administering procainamide on a 3- or 4-hourly basis even in hospital is readily apparent. It is magnified when the drug is prescribed on an outpatient basis. A sustained release preparation of procainamide would have major advantages.

The object of the present study was to estimate the plasma levels obtained using a sustained release preparation of procainamide in patients with acute myocardial infarction. Furthermore, a comparison was made between these results and those obtained in a similar group of patients with conventional procainamide tablets.

Patients and Methods

Patients who were admitted to the coronary care unit of Hammersmith Hospital and in whom a diagnosis of myocardial infarction was made on W.H.O. criteria were eligible for the study. Patients with severe heart failure, second-degree, or complete heart block, or pre-existing renal disease were excluded. Patients who fulfilled these criteria and who had required a lignocaine infusion to control ventricular tachyarrhythmias in

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the initial 48 hours after admission, were then treated with either conventional procainamide tablets[1] or sustained release procainamide[2].

Conventional procainamide tablets were administered as follows:

1) 9 patients received a loading dose of 1g procainamide.
2) 13 patients received 375 mg procainamide 3-hourly.

Sustained release procainamide was administered as follows:

1) 6 patients received a single loading dose of 1·5g procainamide.
2) 15 patients received a loading dose of 2g procainamide.
3) 8 patients received a loading dose of 2g procainamide followed by 1·5g 8-hourly as a maintenance dose.
4) 5 patients received a loading dose of 2g procainamide followed by 1·5g at 4 hours and then 1·5g 8-hourly as a maintenance dose.

In the early phase of complicated myocardial infarction, blood urea may rise and the creatinine clearance may fall (Hutton *et al.*, 1970). Since procainamide is primarily excreted in the urine unchanged and its clearance correlates with creatinine clearance, the studies reported here have been limited to patients in whom the blood urea at the time of study was normal.

The nature of the study was explained to all patients and their consent obtained.

Blood samples

When loading doses of conventional procainamide were being administered the initial samples were taken at half-hourly intervals in order to identify early peaks; subsequently, hourly samples were taken for a total of at least 6 hours. With maintenance therapy on standard tablets, samples were taken at hourly intervals for 6 hours when 375 mg procainamide was administered 3-hourly. These samples were taken at least 48 hours after the initiation of maintenance therapy when stable blood levels should have been achieved. With the sustained release procainamide preparation, the effects of single loading doses were followed at hourly intervals for at least 8 hours. With maintenance therapy after an initial dose, samples were obtained at 4-hourly intervals for at least 48 hours, omitting one sample in the early morning when the patients were asleep.

Plasma procainamide estimation

5 ml venous blood was withdrawn into lithium heparin tubes and centrifuged within 4 hours. The plasma was then removed and stored at 4°C until analysis within the next 5 days. Procainamide is not readily decomposed by plasma enzymes (Moe and Abildskov, 1970). The plasma concentration was measured spectrofluorometrically as described by Koch-Weser *et al.* (1969). The percentage recovery was calculated for each patient by the inclusion of a known standard concentration of procainamide. The reliability of the method was tested by analysis of samples from a plasma pool with a known procainamide content. This gave an average recovery of 95 ± 1·7 per cent.

Results

A) Conventional procainamide tablets

With the initiation of therapy it is important to reach therapeutic plasma levels early. Koch-Weser has stressed the value of using a loading dose and suggested that twice the oral maintenance dose is appropriate (Koch-Weser *et al.*, 1969). In the present study a 1g loading dose was not adequate and only just attained therapeutic levels (see Fig. 1). The time taken to achieve this level is 117 ± 27 minutes.

The plasma levels achieved after receiving 375 mg of procainamide for 48 hours administered as a tablet 3-hourly in 13 patients are shown in Fig. 2. It is apparent that in this study 375 mg conventional procainamide given 3-hourly did not maintain adequate therapeutic plasma levels during the period of observation.

B) Sustained release procainamide

Six patients were given a 1·5g loading dose of sustained release procainamide. A 2g loading dose was given to a further 15 patients. Therapeutic levels were reached within two hours of initiation of the therapy (Fig. 3). The peak level after 2g sustained release procainamide was 7·4 ± 0·4 μg/ml at 160 ± 16 minutes, and this compared with 6·0 ± 0·9 μg/ml at 117 ± 27 minutes after 1g conventional procainamide tablets. A single initial

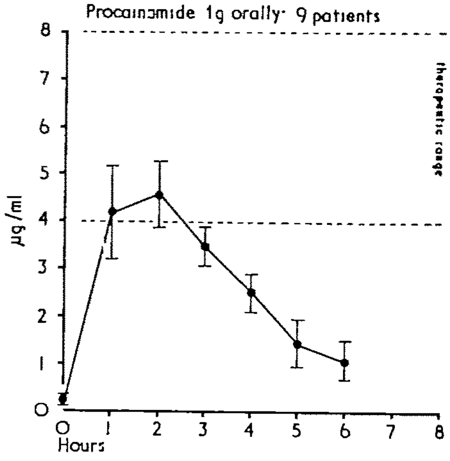

FIG. 1 *Plasma levels of procainamide after 1g loading dose of conventional tablets.*

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[1] Pronestyl (Squibb).

[2] Procaine Amide Durules (AB Hassle).

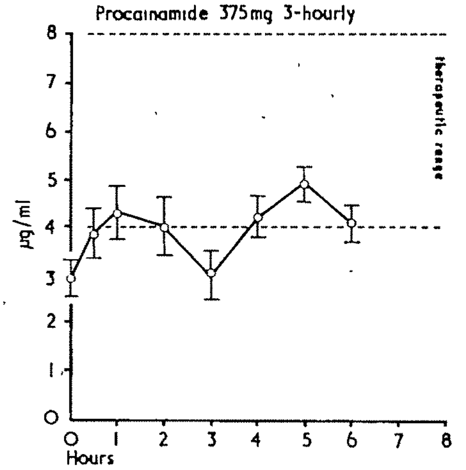

FIG. 2 *Plasma levels of procainamide in 13 patients who received 375 mg of conventional tablets 3-hourly for at least 48 hours.*

dose of 2g sustained release procainamide maintains the plasma level in the therapeutic range for 5 to 6 hours in the first 8-hour period without entering the toxic range. When 1·5g of the sustained release preparation was given, the peak plasma level of 7·1 ± 1·0 μg/ml was achieved in 210 ± 46 minutes.

When a maintenance dose of 1·5g was administered 8-hourly after a 2g loading dose adequate plasma levels were achieved continuously up to 48 hours with the exception of a short period before the first maintenance 1·5g dose as shown in Fig. 4.

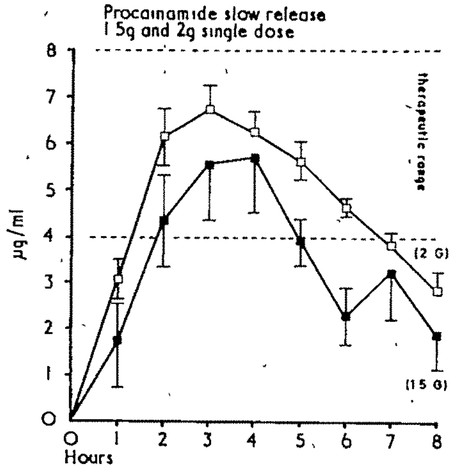

FIG. 3 *Plasma levels of procainamide after administration of 1·5g (6 patients) and 2g (15 patients) of sustained release preparation.*

In an attempt to avoid the short period outside the therapeutic range after the 2g loading dose and before starting maintenance therapy, 5 patients were studied in whom 1·5g were given 4 hours after the initial 2g loading dose and then an 8-hourly maintenance dose of 1·5g started. This, however, had the effect of raising the plasma levels towards the toxic range.

Side effects

There were no major side effects with conventional or sustained release procainamide in the short-term studies performed here.

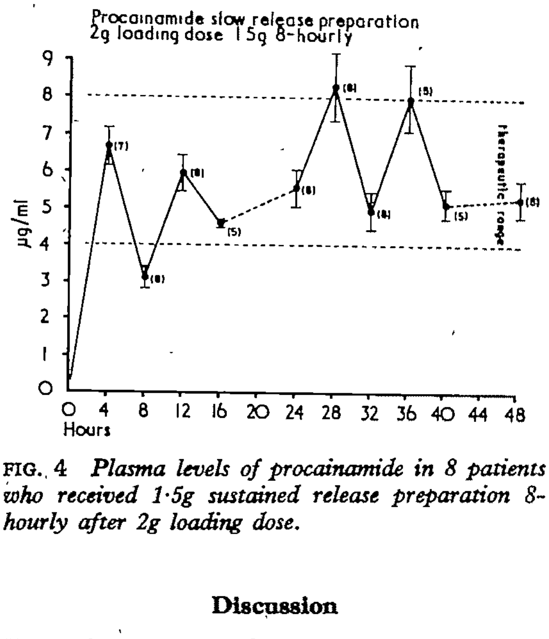

FIG. 4 *Plasma levels of procainamide in 8 patients who received 1·5g sustained release preparation 8-hourly after 2g loading dose.*

Discussion

The original work of Koch-Weser related the plasma levels of procainamide to its therapeutic and toxic side effects and formulated a 3-hourly regimen in order to achieve stable and effective plasma levels (Koch-Weser *et al.*, 1969; Koch-Weser, 1971; Koch-Weser and Klein, 1971). In the present study the practical value of this regimen was not confirmed since in patients weighing 54·4 to 90·7 kg, conventional procainamide capsules in a dose of 375 mg given 3-hourly failed to maintain adequate plasma levels. Shaw and co-workers found that 500 mg conventional procainamide given 4-hourly was also unsatisfactory in 36 per cent of patients (Shaw *et al.*, 1974). It is not easy to justify the use of a prophylactic drug on a 3-hourly basis for anything but a limited period.

For these reasons we concluded that in terms of the plasma level achieved conventional procainamide therapy is impracticable and unsatisfactory in the management of patients with ventricular arrhythmias after myocardial infarction.

The formulation of procainamide as a sustained release preparation removes the sharp peaks in blood plasma level that may be observed one or two hours after conventional procainamide and which are potentially toxic. The dissolution of sustained release procainamide persists over 6 hours *in vitro* compared with 5 minutes with the conventional tablets (C. Graffner, G. Johnsson, and J. Sjogren, 1973, personal communication). It is apparent that 2g of the sustained release preparation followed by 1·5g given 8-hourly orally will provide plasma levels within the therapeutic range from 2 hours onwards. There is a brief fall below the therapeutic range just before administration of the first maintenance dose. In an effort to avoid this the first maintenance dose of 1·5g was administered at 4 hours instead of 8 hours but this produced potentially toxic plasma levels, though side effects themselves were not recorded.

The sustained release preparation has not been used during the first 48 hours after infarction. During this time absorption and excretion of the drug may be influenced by minor and transient degrees of heart failure. It may be predicted that as with the conventional preparation some reduction in dose would be appropriate for patients with heart failure or raised blood urea. Measurement of plasma levels is necessary in these patients in order to achieve the appropriate dosage.

The period of administration of the sustained release preparation was 48 hours. During this period no side effects were noted. It is possible that either the serological or clinical manifestations of the systemic lupus erythematosus syndrome, which are known to be potential complications of conventional procainamide therapy (Fakhro, Ritchie and Lown, 1967; Molina *et al.*, 1969; Kosowsky *et al.*, 1973) may develop with prolonged use of the sustained release preparation. The changes are reversed by discontinuing therapy but serological testing and clinical observation to detect the appearance of this syndrome would be mandatory if prolonged therapy was thought to be justified.

The present study indicates that when sustained release procainamide is administered to patients 48 hours after the onset of myocardial infarction stable and therapeutic blood levels can be consistently achieved using 8-hourly administration. It is suggested that such a sustained release preparation should be used whenever the drug is indicated for oral therapy in patients after myocardial infarction. A controlled study of its therapeutic value in the prevention of recurrent ventricular arrhythmias and particularly recurrent ventricular fibrillation during the first three months after myocardial infarction would be justified.

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Echocardiographic assessment of mitral valve calcification

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The mitral valve was assessed by echocardiography in 20 patients, aged 27 to 67 years, who subsequently underwent mitral valve replacement. After removal, the mitral valve cusps were examined by direct measurement, radiography, and quantitative calcium extraction.

Increased thickness of the E-F echo was found where calcification or fibrosis was present, differentiation by echocardiography alone being unreliable. However, multiple dense parallel E-F echoes were found in all 10 patients with more than 80 milligrammes of calcium in the valve, while a single thin E-F echo indicated the absence of significant calcification or fibrosis.

This study was undertaken primarily to test the clinical impression that dense E-F echoes denote calcification of the mitral leaflets. The basis of the study was the comparison of preoperative echocardiographic measurements with the operative findings and with the pathological findings in the removed valves, but correlation with the fluoroscopic appearances was also sought.

Subjects and methods

Studies were made on 11 male and 9 female patients aged 27 to 67 years (mean 51 years). Calibrated mitral echograms were recorded, by polaroid photography of the Ekoline 20 ultrasonoscope, shortly before operation (mitral valve replacement) in each case. The technique was that described by Feigenbaum (1972), a C-10 transducer being used. The width of the E-F echo ('E-F thickness') was measured, in the plane of the ultrasonic beam, at three points in each echogram, viz. at the E-point, at the F-point, and at a point midway between the two (Fig. 1).

The degree of any mitral valve calcification seen at preoperative fluoroscopy was graded as slight (1), moderate (2), or heavy (3). Calcification and fibrosis of the mitral valve were subjectively assessed at the time of operation as mild (1), moderate (2), or extensive (3).

After removal, the mitral valve apparatus was x-rayed (Fig. 2) at a tube-film distance of 100 cm and any calcification seen was graded 1 to 3. The thickness of each leaflet was measured with a micrometer at the middle of its free edge. The degree of any fibrosis present was scored 1 to 3.

The valve was then placed in calcium-free fixative and suspended in a known volume of Custer's decalcifying fluid for 72 to 96 hours. The amount of calcium extracted was estimated by fluorimetry.

Correlation between the *in vivo* and *in vitro* data was sought, using standard statistical methods.

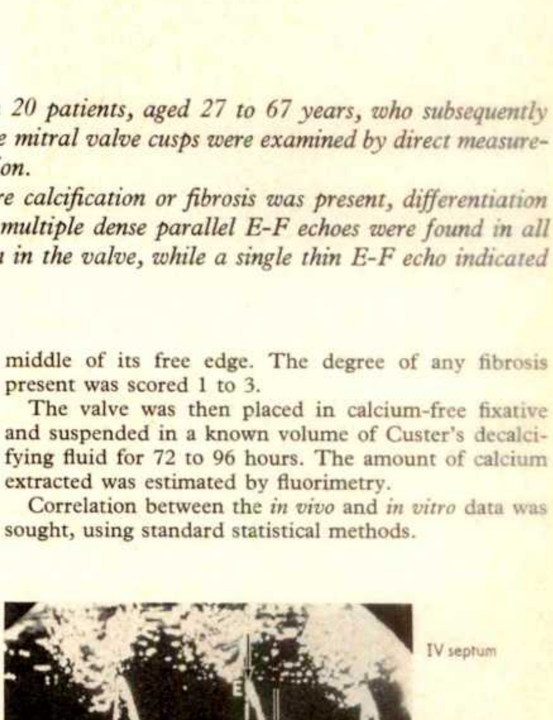

FIG. 1 *Mitral echogram showing points (arrows) of measurement of E-F echo thickness and also features of mitral regurgitation from ruptured chordae (D-E amplitude = 45 mm, rapid E-F slope of normal thickness with discordant mitral echoes in systole).*

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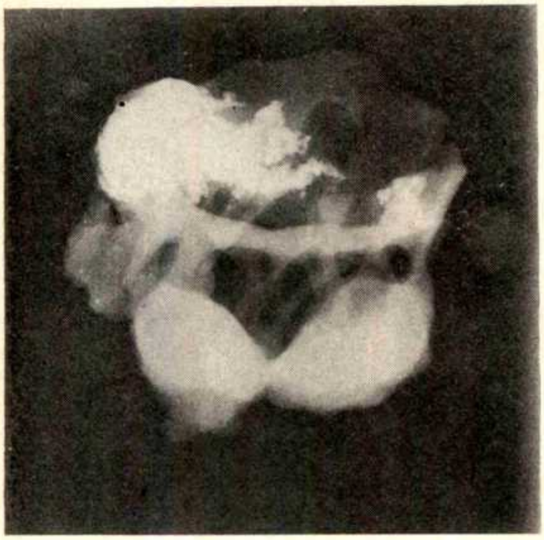


FIG. 2 *X-ray film of mitral valve apparatus showing heavy and slight calcification in the anterior and posterior leaflets respectively.*

Results

Table 1 shows the fluoroscopic and operative findings and diagnostic data. Table 2 shows the echocardiographic data and *in vitro* details of the mitral valve pathology. There was close correspondence between the surgeon's and pathologist's assessment of the degree of fibrosis. The E-F echo was regarded as dense if its thickness exceeded 2·5 mm, the range of this measurement in 30 normal subjects (aged 16 to 55 years) being 0·5 to 2·5 mm.

None of the 3 patients with non-rheumatic mitral valve disease had dense E-F echoes and none had calcification of the cusps.

Some calcium was extracted from the valve in 15 of the 17 patients with rheumatic heart disease. All had dense E-F echoes. In 9 instances the amount of calcium extracted was substantial (145 to 625 mg), and the preoperative mitral echograms for all these patients showed multiple dense E-F echoes (Fig. 3); fluoroscopy had also detected calcification preoperatively in these 9 and the surgeon had reported moderate or heavy calcification of the cusps in each case.

In 5 of the remaining 6 patients with dense E-F echoes in their echocardiograms (Fig. 4), there was less than 20 mg calcium in the valves, which were moderately or densely fibrosed. In none of these was calcification reported at preoperative fluoroscopy or by the surgeon. One 62-year-old patient (Case 17), with multiple dense E-F echoes, had 83 mg calcium in her valve; fluoroscopy, but not the surgeon, had failed to detect it.

Neither of the 2 patients (Cases 1 and 3) with rheumatic heart disease but E-F echoes less than 2·5 mm thick had calcified valves.

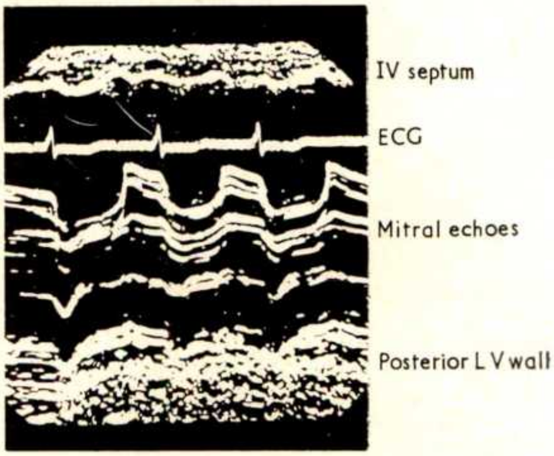


FIG. 3 *Mitral echogram showing multiple dense (3 mm) E-F echoes with reduced amplitude of motion (D-E = 12 mm).*

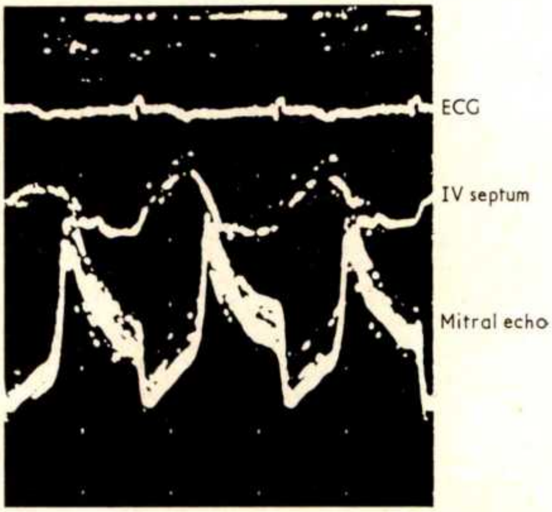


FIG. 4 *Mitral echogram showing dense (3 mm) E-F echo with D-E amplitude of 25 mm.*

TABLE 1 *Fluoroscopic and surgical assessment of mitral valve*

Case No.	*Age (yr)*	*Sex (M/F)*	*Diagnosis*	*Screening for mitral calcification*	*Operative findings*	
					Calcification	*Fibrosis*
1	44	M	Rheumatic MS, MR	Nil	Nil	3
2	56	M	Rheumatic MS, MR	1	3	1
3	48	M	Rheumatic MR, MS	Nil	Nil	2
4	48	M	Rheumatic MS, MR	1	2	1
5	41	M	Rheumatic MS, MR	3	3	1
6	60	M	Rheumatic MS, MR	1	2	2
7	55	M	Rheumatic MS, MR	2	3	1
8	42	M	Rheumatic MS, MR	1	2	1
9	48	F	Rheumatic MR, MS	Nil	Nil	3
10	62	F	Rheumatic MR, MS	1	2	1
11	57	F	Rheumatic MS, MR	1	3	1
12	63	F	Rheumatic MR, MS	Nil	Nil	3
13	55	F	Rheumatic MS, MR	2	2	2
14	33	F	Rheumatic MS, MR	Nil	Nil	2
15	48	F	Rheumatic MR, MS	Nil	Nil	2
16	45	F	Rheumatic MR, MS	Nil	Nil	2
17	62	F	Rheumatic MR, MS	Nil	1	2
18	67	M	Non-rheumatic MR, IHD	Nil	Nil	Nil
19	61	M	Non-rheumatic MR (myxomatous degeneration)	Nil	Nil	1
20	27	M	Marfan's syndrome AR, MR	Nil	Nil	1

MS=mitral stenosis. MR=mitral regurgitation. AR=aortic regurgitation. IHD=ischaemic heart disease. 1=slight. 2=moderate. 3=heavy.

TABLE 2 *Mitral echographic and pathological data*

	Mitral echographic features			*Mitral valve pathology*				
Case No.	*Description of E-F echo*	*D-E amplitude (mm)*	*E-F thickness* (mm)*	*Cusp thickness (mm)*		*X-ray Ca†*	*Extraction of Ca (mg)*	*Fibrosis*
				Ant.	*Post.*			
1	Multiple	25	2·0	2·6	3·9	Nil	Nil	3
2	Multiple	20	3·0	3·0	4·0	3	445	1
3	Single	45	2·0	2·0	3·0	Nil	Nil	2
4	Multiple	25	4·0	3·7	3·0	3	240	1
5	Multiple	20	4·0	11·0	3·0	3	625	1
6	Multiple	18	3·0	5·0	5·0	3	190	2
7	Multiple	12	3·0	10·0	8·0	3	430	1
8	Multiple	18	3·0	2·6	1·8	3	260	1
9	Multiple	18	4·0	3·5	4·8	1	7	3
10	Multiple	16	3·0	8·0	8·0	2	145	2
11	Multiple	22	3·0	6·0	2·2	3	265	1
12	Multiple	16	2·7	6·0	3·0	1	5	3
13	Multiple	20	3·0	4·0	6·0	2	170	1
14	Single	18	3·0	3·0	4·0	1	2·5	2
15	Single	22	3·0	4·0	3·0	1	18	2
16	Single	18	2·6	3·0	4·2	1	14	2
17	Multiple	15	3·0	4·0	2·8	2	83	2
18	Single	23	1·5	1·4	1·7	Nil	Nil	1
19	Single	35	1·5	1·5	1·3	Nil	Nil	Nil
20	Single	45	1·5	3·0	4·0	Nil	Nil	1

*No significant difference was found between the three points measured.. †Degree of calcification seen in film of removed mitral valve. 1=slight; 2=moderate; 3=dense.

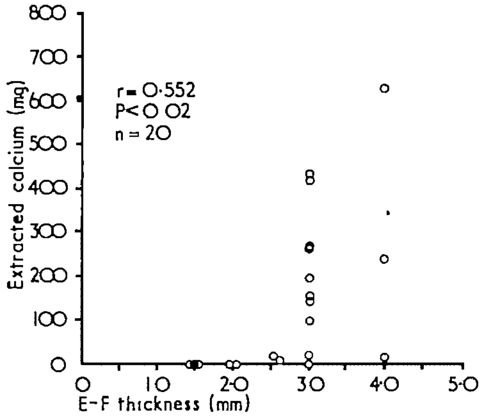


FIG. 5 *Correlation of amount of calcium extracted from mitral valve with echocardiographic E-F thickness.*

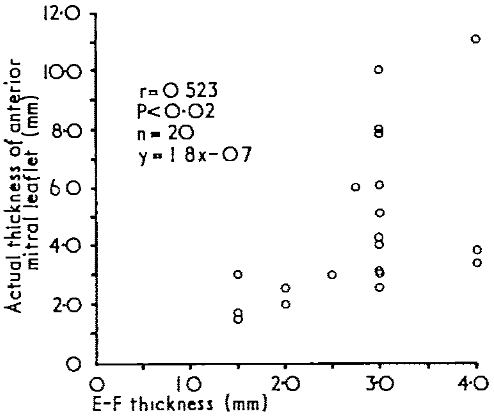
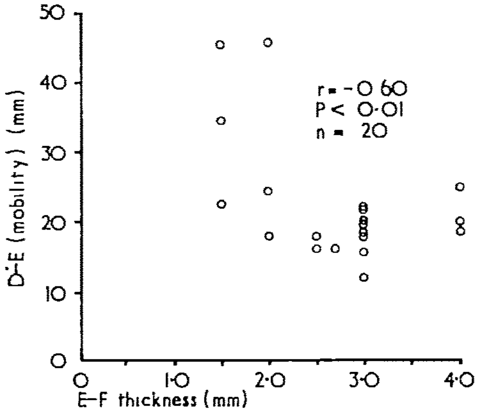


FIG. 6 *Correlation of echocardiographic E-F thickness with actual thickness of anterior mitral leaflet.*



In the group of 20 patients as a whole, the measured thickness of the E-F echo correlated significantly at the 5 per cent level with *(a)* the degree of mitral calcification as assessed fluoroscopically (r=0·48), *(b)* the amount of calcium extracted from the valve (r=0·55, P<0·02) (see Fig. 5), and *(c)* the actual thickness of the anterior mitral leaflet (r=0·52, P<0·02) (see Fig. 6).

Significant negative correlation was found between E-F thickness and D-E amplitude (r=−0·60, P<0·01) (see Fig. 7).

Discussion

Thickening of the E-F echo of the echocardiogram is found where the mitral valve is calcified or distinctly fibrosed. Both processes reduce valve mobility. The findings in this study amplify those of Joyner *et al.* (1965). Substantial amounts of calcium in the valves were always associated with multiple roughly parallel E-F echoes in this series, though the presence of such echoes did not guarantee the existence of important calcification. Heavy calcification and dense fibrosis of the valve appear not to coexist. The thickness of the E-F echo is only an approximate guide to the true thickness of the anterior mitral leaflet, large underestimates being not infrequent. This finding should occasion no surprise in view of the difficulties of standardizing the ultrasound technique and the uneven distribution of the pathological changes in the valve.

We wish to thank Dr. H. A. Fleming for allowing us to include his patients in this study, Messrs. B. B. Milstein and T. A. H. English for the surgical assessments, Drs. G. I. Verney and C. R. Flower for fluoroscopies, and Mr. R. Hanka for help with statistical analysis.

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FIG. 7 *Correlation of echocardiographic E-F thickness with D-E amplitude.*

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Failure of ST segment elevation to predict severity of acute myocardial infarction[1]

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Praecordial ST segment elevation was measured at 35 electrode positions in each of 40 patients admitted to a coronary care unit after acute transmural anterior myocardial infarction. Serial praecordial electrocardiographic maps were recorded to determine (a) the time course as well as reproducibility of measurements of ST segment alterations, and (b) the degree of correlation between the magnitude of ST segment elevation and the severity of infarction, as assessed clinically or by sequential estimations of serum creatine kinase activity. Large variations in ST segment elevation were found in different patients with a comparable degree of myocardial damage, and at intervals of as little as four hours in the same patient. These variations were greater than could be explained by technical factors, and were not related to apparent changes in the patients' clinical status. The patterns of release of myocardial creatine kinase showed that the time course of ST segment elevation was longer than the period of myocardial necrosis. No correlation was found between the myocardial infarct size as determined by enzyme release and the highest levels of ST segment elevation recorded. The findings suggest that ST segment elevation as measured by praecordial electrocardiographic mapping does not constitute a reliable index of the size or severity of myocardial infarcts in man.

Though elevation of the ST segment of the electrocardiogram has been recognized for many years as one of the classical signs of acute myocardial infarction (Eppinger and Rothberger, 1909), the electrophysiological correlates of ischaemic injury were not established until intracellular potentials could be recorded from the intact heart. It is now known that ischaemia following coronary artery occlusion leads to an acceleration of repolarization, with loss of resting membrane potential, which results in ST segment elevation in the surface electrocardiogram (Samson and Scher, 1960; Prinzmetal *et al.*, 1961). Of particular interest recently has been the report of Maroko and his associates (1971) that there is a significant correlation between the magnitude of epicardial ST segment elevation 15 minutes after experimental coronary occlusion in dogs, and infarct size as determined by loss of myocardial creatine kinase (CK) activity or histological changes 24 hours later. The possibility has thus arisen that quantification of praecordial ST segment elevation by a simple non-traumatic technique in patients might prove of value for the assessment of size and severity of the initial ischaemic damage (Maroko *et al.*, 1972a; Reid, Pelides, and Shillingford, 1971; Neilsen, 1973; Maroko, 1974), and that serial measurements might be used to evaluate subsequent progress (Reid *et al.*, 1974) or test the effectiveness of drugs in altering the extent of ischaemic injury (Pelides *et al.*, 1972; Maroko *et al.*, 1973).

The present study was undertaken to investigate further the value of ST segment elevation as a clinical guide to infarct size in patients in a coronary care unit. The main aims were to study the relation between the extent of ST elevation and clinical indices of severity of infarction, the time course of ST segment changes, and the relation between ST elevation and infarct size estimated by calculations of total CK release from four-hourly determinations of serum enzyme activity (Shell, Kjekshus, and

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Sobel, 1971; Sobel *et al.*, 1972; Norris *et al.*, 1975). However, initial results showed such wide variations in the extent of ST elevation from patient to patient, and at different times in the same patients, that it also became necessary to investigate the reproducibility of measurements.

Methods

Electrocardiographic mapping

A modified version of the electrode blanket described by Maroko and colleagues (1972a) was used. This was a plastic fabric template measuring 45 × 25 cm in which 35 square holes were cut, in 7 vertical and 5 horizontal rows. The holes measured 2 × 2 cm, the distance between centres of horizontal rows being 4 cm, and between successive centres of the second to seventh vertical rows 4·5 cm. Centres of the first and second vertical rows, which lay to the right and left of the sternum respectively, were 7 cm apart. The template was placed horizontally, with the top right hand hole in the second intercostal space, 2 cm lateral to the right sternal border. The first vertical row of holes lay to the right of the sternum and the last in the mid-axillary line; the blanket thus covered the praecordial area overlying the anterior and lateral surfaces of the left ventricle. Between four and six QRS complexes from each of the 35 sites were recorded with a metal suction electrode 1·5 cm in diameter attached to the V lead of a standard electrocardiograph and recorded at a sensitivity of 1 cm=1 mV, and at a paper speed of 25 mm per second. A representative complex with a stable baseline was selected from each of the 35 positions, cut out, and pasted on a card. The ST segment elevation from each position was recorded to the nearest 1 mm, excluding those with elevations of less than 2 mm. Where the ST segment was sloping, elevation at the mid-point was taken as the height of ST elevation for that complex. Each 'map' was analysed (in many cases, independently by two observers) for the total ST elevation from all 35 positions (ΣST), and the number of positions showing ST elevation of 2 mm or greater. The QRS duration was checked in all cases, since delayed intraventricular conduction caused by complete or partial bundle-branch block can obscure ischaemic ST elevation (Beckwith, 1970). Cases in which the QRS duration was greater than 0·08 s were therefore excluded from analysis; in the event, it became necessary to exclude only one case because of abnormal QRS prolongation. Since ST segment elevation caused by inferior infarction cannot be detected using praecordial electrode positions, studies were carried out only on patients with anteroseptal or anterolateral infarction, as shown on the standard electrocardiogram.

Measurement of total CK release

Samples of peripheral venous blood were analysed for CK activity four-hourly, and total CK release was calculated by our modification (Norris *et al.*, 1975) of the method of Sobel and colleagues (1972). In our method, accuracy of the calculation of total CK release is improved by individual measurement of CK degradation rate for each patient.

Patients studied

Forty patients with transmural anterior infarction and five normal subjects were studied. The following investigations were made, most patients being included in more than one group:

i) Normal subjects A single map was recorded on each of 5 subjects aged between 40 and 70 years, who had no clinical evidence of heart disease.

ii) Reproducibility studies Reproducibility of recordings was investigated in 12 patients as follows:

a) Two QRS complexes with stable baseline were selected from each praecordial electrode position and were mounted separately, so that ΣST could be measured using different complexes from the same record (beat-to-beat variation). Ten such comparisons were made on 5 patients.
b) A possible effect of changes in skin resistance on ΣST was investigated by making 2 consecutive records from each position after removal and immediate replacement of the suction electrode (electrode placement variation). Ten such comparisons were made on a further 5 patients.
c) Mapping was repeated in the same patient after one hour (hour-to-hour variation). This was done in 12 patients who were free from chest pain and arrhythmias, 1 to 3 days after the onset of infarction.

iii) Correlation of ST elevation with clinical indices of severity Clinical severity of infarction, assessed by the arterial blood pressure and pulse rate (recorded routinely by the nursing staff), and the presence or absence of evidence of pulmonary venous hypertension, interstitial oedema, or pulmonary oedema in a chest *x*-ray taken during the acute phase (Norris *et al.*, 1969), was compared with the maximum recorded ΣST in 29 patients. These patients had a mean of 6 (range 2 to 19) maps taken at intervals of 1 to 2 days, the first being recorded within 24 hours of onset of the most severe pain.

iv) Time course of ST elevation The time course of ST elevation during 1 week after the onset of infarction, and its relation to the duration of CK release from the infarct, was studied in 16 patients in whom 4-hourly measurements of serum CK activity had been made, and in whom maps were available for at least 4 of the following 5 periods after the onset of infarction: 0 to 12 hours, 1, 2, 3 to 4, and 5 to 7 days. The time course over the first 24 hours was examined further in 11 patients by comparing the ST elevations recorded within 6 hours of onset of infarction with the ST elevations at 7 to 24 hours after the onset.

v) Correlation of ST elevation with total enzyme release The highest recorded value for ΣST was compared with the total release of CK (IU/ml serum) in 15 patients in whom the latter integral could be calculated accurately (Norris *et al.*, 1975).

vi) Effect of beta-adrenergic receptor blockade on ST elevation during recovery from infarction In order to determine whether ΣST could be altered after completion of the infarct, at a time when infarct size could presumably not be altered, practolol 20 mg was given intravenously to 8 patients at a mean time of 9 days (range 5 to 13 days) after the onset of infarction. Maps were recorded immediately before, and 1 hour after the injection, and ΣST and the heart rate were measured. Approximately 6 maps had already been recorded on these patients, who were all convalescing and had no clinical evidence of reinfarction at the time of the study.

Results

i) Normal subjects

No ST segment elevation was found in the 5 normal subjects.

ii) Reproducibility studies

Results of these measurements are shown in Table 1. The mean variation of ΣST measured from different QRS complexes in 10 comparisons (beat to beat variation) was 4·7 per cent (range, 0 to 17%), while the mean variation in 10 comparisons in which the suction electrode was removed and then immediately reapplied (electrode placement variation) was 8·3 per cent (range, 2 to 17%). When recordings were made one hour apart in 12 patients, the variation was greater (mean variation, 14·3%; range, 0 to 47%). In 7 patients, the hour-to-hour variation was within the range which we found with beat-to-beat and electrode placement variation, but in 5 patients was greater (22 to 47%). These results suggested that the pronounced variations in ΣST which occurred within hours or days in individual patients (see below) were in most cases the result of real changes, and were not caused by random beat-to-beat variations or by differences in technique of making the recordings.

iii) Clinical correlation

No relation was apparent between arterial blood pressure, pulse rate, and ΣST when different patients were compared; nor were variations in ΣST within the same patient related in any constant way to changes in blood pressure or heart rate. Furthermore, there was no relation between the clinical severity of infarction, judged by the degree of pulmonary venous hypertension present in chest *x*-rays taken during the acute phase, and the highest recorded value for ΣST. In 11 patients without pulmonary congestion, the mean maximum ΣST was 76 mm (range 19 to 130 mm), while in 9 patients with interstitial or frank pulmonary oedema, the mean maximum ΣST was 55 mm

TABLE 1 *Reproducibility of ST segment elevation measurements*

Case No.	*Beat-to-beat variation*			*Electrode placement variation*			*Hour-to-hour variation*		
	ΣST_1	ΣST_2	*% Variation*	ΣST_1	ΣST_2	*% Variation*	ΣST_1	ΣST_2	*% Variation*
1	36	35	3				36	58	47
	57	58	2						
2	30	31	3				30	24	22
	47	47	0						
3	154	144	7				149	145	3
	142	148	4						
4	65	55	17				60	55	9
	55	55	0						
5	54	53	2				54	68	23
	71	65	9						
6				128	136	6	132	126	5
				123	128	4			
7				85	92	8	88	88	0
				85	91	7			
8				50	52	4	51	38	29
				41	36	13			
9				54	64	17	59	57	3
				55	58	5			
10				56	55	2	56	59	5
				54	64	17			
11							96	120	22
12							76	73	4
Mean ± 1 SD			4·7±5·2			8·3±5 5			14·3±14·3

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(range 9 to 112 mm). In 9 patients with pulmonary venous congestion but no oedema, the mean maximum ΣST was 68 mm (range 12 to 118 mm). Substitution of the number of electrode positions showing ST elevation of 2 mm or greater for maximum ΣST did not improve these correlations.

iv) Time course of ST elevation

The time course of ST elevation in 16 patients in whom serial records were available for the first week after onset of infarction is shown in Fig. 1. There was a very wide variation in ΣST between individual patients, with no important difference in the range of values for ΣST at different times within the first week. The protracted course of ST elevation, compared with the duration of myocardial necrosis, as judged by the time course of CK release into the circulation, is also shown in Fig. 1. ST elevation persisted, in general, for a considerably longer period than did CK release.

Changes in 11 patients in whom maps were recorded within 6 hours (mean 4·5 hours) of the onset and again at 7 to 24 hours (mean 16 hours) after the onset are shown in Table 2. ΣST was less on the second occasion in 6 cases, greater in 3, and the same in 2. The mean ΣST at 7 to 24 hours was 39 mm; because of the large variation, this was not significantly lower than the mean ΣST of 58 mm at 3 to 6 hours.

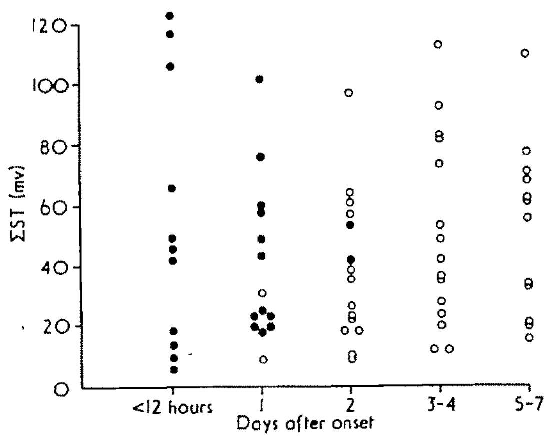

FIG. 1 *Temporal changes in ST segment elevation are shown in 16 patients with transmural anterior infarction, in whom ST segment maps were available for at least 4 of the 5 periods indicated on the horizontal axis. Closed circles refer to observations made during the period of creatine kinase release, while open circles refer to those made after completion of enzyme release. There is no obvious tendency for ST elevation to decrease at 5 to 7 days after onset of infarction, nor after cessation of enzyme release.*

TABLE 2 *Changes in ST segment elevation during 24 hours after onset of transmural anterior infarction*

Case No.	*ΣST (mv)* *Within 6 hours*	*7 to 24 hours*	
13	19 (6)	19 (14)	
14	6 (4)	20 (23)	
15	9 (4)	9 (24)	
16	107 (4)	25 (24)	
17	49 (6)	33 (9)	51 (15)
18	130 (3)	118 (7)	
19	68 (4)	22 (10	40 (15)
20	66 (5)	39 (9)	21 (16)
21	123 (4)	21 (8)	
22	46 (4)	18 (10)	
23	15 (6)	31 (10)	68 (14)

Figures in parentheses refer to time after the onset of chest pain in hours.

The striking differences between patients are shown by the four illustrative cases in Fig. 2 in which the course and extent of myocardial necrosis, as judged by the release of CK into the circulation, is compared on the same time-scale with the course of ST elevation. It should be noted that the closed circles relate to the total of CK release into the circulation which had occurred up to the time shown in the graph (Sobel *et al.*, 1972; Norris *et al.*, 1975); they do not represent the serum levels which are in fact declining in an exponential fashion when total release reaches a plateau.

Fig. 2 shows that in some patients a great reduction in ST elevation occurred during the acute phase of CK release (Fig. 2A), while in others a gradual increase in elevation occurred during the first few days even though the rate and extent of CK release was small (Fig. 2B). In other cases ΣST fell and rose again (Fig. 2C), or remained constant and of slight degree, in patients with large infarcts as judged by CK release (Fig. 2D).

v) Correlation of ST elevation with total enzyme release

The relation between the maximal figures for ΣST and myocardial infarct size assessed from four-hourly measurements of serum CK activity is shown in Fig. 3. No significant correlation is demonstrated, and the correlation was not improved by substitution of the figures for the number of electrode positions showing ST elevation for ΣST.

vi) Effect of beta-adrenergic reception blockage after completion of infarction

When practolol 20 mg was given intravenously to 8 patients who were convalescent after myocardial infarction, and the epicardial map repeated after

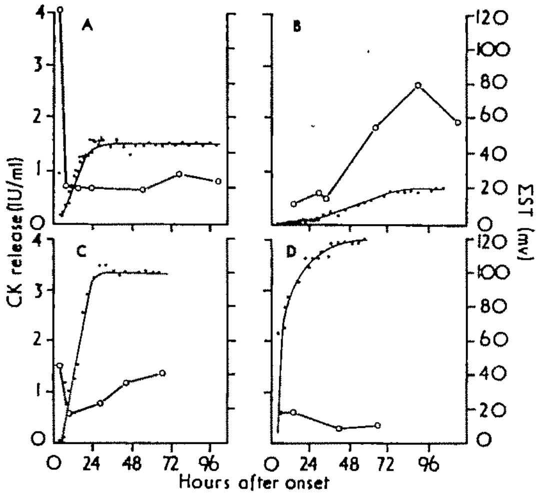

FIG. 2 *Four illustrative cases of transmural anterior infarction are shown, contrasting the sum of ST elevations from 35 praecordial positions (ΣST) (open circles) with the development of myocardial necrosis, as judged by the integral of creatine kinase (CK) activity released into the circulation (closed circles). This latter integral relates to total enzyme release, and not to the serum levels (see text). The plateau on the total enzyme release curve denotes cessation of enzyme release, while the slope of the curve before the plateau indicates the velocity of release; the height of the plateau is considered to be an index of myocardial infarct size. Case (A) : ΣST drops from 123 mm to 21 mm over 4 hours, despite continuing myocardial necrosis, evidenced by a steeply rising enzyme curve. Case (B) : a considerable increase in ST segment elevation has occurred 3 to 4 days after the onset, despite a comparatively small extent and rate of enzyme release. Case (C) : increasing ST segment elevation has occurred from 1 to 3 days, though myocardial necrosis, judged from the plateau of total CK release, has ceased. Case (D) : ST segment elevation is relatively constant but minimal, though the infarct is large, judged from the enzyme curve. The development of pulmonary oedema in this patient, who did not have pre-existing heart disease, suggested that enzyme release was a better predictor of the severity of infarction than was ST segment elevation in his case.*

one hour, there was a consistent reduction in ΣST, accompanied by a 10 per cent reduction in heart rate (Fig. 4). The mean change in ST elevation was –23 per cent (range –10% to –47%), which was significantly different from the change which was found to occur in one hour in the patients shown in Table 1 ($t=3{\cdot}17$; $P<0{\cdot}01$).

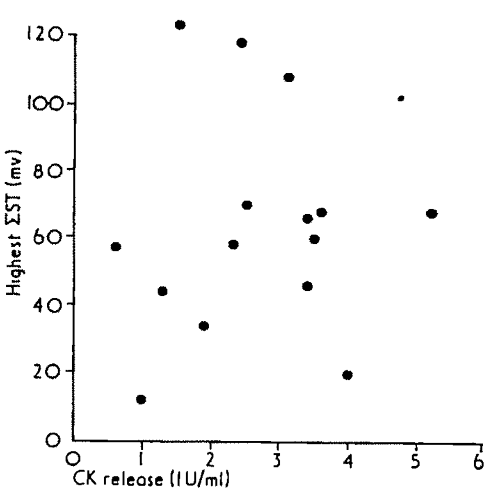

FIG. 3 *The highest recorded ΣST is plotted against total release of creatine kinase (CK) activity in 15 patients. No correlation was apparent between these measurements.*

Discussion

Our studies in patients with transmural anterior myocardial infarction have not revealed a simple relation between the magnitude of praecordial ST segment elevation and clinical or biochemical indices of severity or size of the infarct. The time course of ST elevation was prolonged beyond the period of myocardial necrosis as judged by the activity of CK enzyme released into the circulation. Moreover, considerable variations in the degree of ST elevation, accompanied neither by changes in clinical status nor in the rate of enzyme release, occurred in individual patients. Our reproducibility studies showed that these alterations were too large to be explained solely by variability in recording techniques, since the temporal changes were, in most cases, outside the range of variation which occurred from beat to beat or with slight alterations in placement of the praecordial electrode.

The results thus emphasize the limitations of the praecordial ST segment mapping technique for the bedside estimation of ischaemic injury in patients with acute anterior myocardial infarction. Since this conclusion is seemingly at variance with results from previously reported experimental (Maroko *et al.*, 1971) and clinical studies (Maroko *et al.*, 1972a; Reid *et al.*, 1974), it is of importance to examine similarities and differences between these and our studies.

Maroko and his colleagues have clearly established that a direct correlation exists between

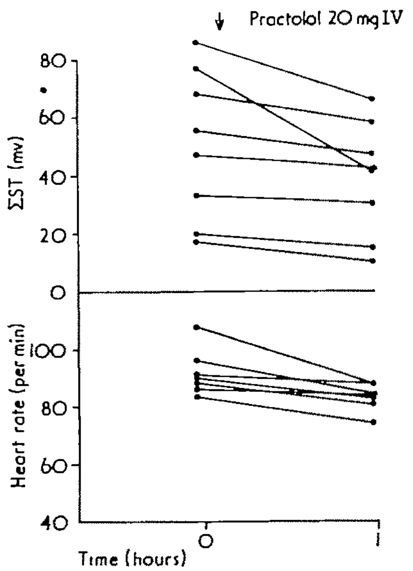

FIG. 4 *The effect of practolol (20 mg intravenously) on ST segment elevation and heart rate is shown in 8 convalescent patients who were studied at a mean of 9 days after the onset of infarction. The fall in ST segment elevation (23%) was significantly different ($P < 0{\cdot}01$) from changes occurring in 12 other patients in whom measurement of ST segment elevation was repeated after one hour without administration of practolol. Heart rate fell by 10 per cent (average of 7 cases).*

the extent of ST segment elevation measured at 15 minutes after experimental coronary occlusion and infarct size measured either by myocardial CK depletion (Maroko *et al.,* 1971) or the severity of tissue necrosis determined both by light and electron microscopy (Maroko *et al.,* 1972b). Extrapolation of these results to the clinical setting may be hazardous for a number of reasons.

First, ST segment elevation is an immediate effect of myocardial ischaemia, but as cells undergo necrosis it is likely that elevation becomes less. Enzyme release, on the other hand, is a manifestation of cellular death, starting approximately 6 hours after the onset of ischaemia, and continuing for 24 to 48 hours (Sobel *et al.,* 1972). In an area of infarcting myocardium both processes may coexist for a time, some cells undergoing necrosis more quickly than others. It is conceivable that ΣST measured at the very onset of infarction in man might correlate more closely with clinical or biochemical indices of severity than ΣST measured after patients have been admitted to a coronary care unit, when infarction is well established. Thus it might be argued that in patients such as those illustrated in our Fig. 2A and D, necrosis of all ischaemic cells had occurred quickly, so that ST elevation (though perhaps present early) declined quickly, followed by a rapid release of CK enzyme. This seems unlikely as a general explanation for our findings, because of the protracted course of ST elevation in many patients (Fig. 1 and 2B and C), and the lack of any clear evidence that ΣST was higher when measured at 3 to 6 (mean 4·5) hours after the onset than at 7 to 24 (mean 16) hours after the onset in the same patients.

Second, the experimental results of Maroko *et al.* (1971) relate to epicardial mapping of a small well-defined infarct involving an accessible part of the free wall of the left ventricle, produced by occlusion of a branch of the left anterior descending coronary artery. In patients, myocardial infarction may be more extensive and diffuse, often involving parts of the heart (e.g. the interventricular septum) not readily accessible to surface electrocardiography. Also, praecordial mapping must be done through the intact chest wall, so that variations in body build or of anatomical positions of the heart may seriously distort comparisons among different patients. For these reasons it would be surprising if a strictly quantitative correlation between praecordial ST elevation and size or severity of infarct was apparent when different patients were compared with one another. However, data did not reveal even a rough correlation between ST segment elevation and the degree of ischaemic damage assessed by clinical and biochemical indices. It might nevertheless be argued that these findings do not negate the value of changes in ΣST in predicting favourable or unfavourable trends in an individual patient. No such trends were, however, suggested by the results of the present study in which large hour-to-hour increases or decreases in ΣST were noted without obvious alterations either in the clinical status or in the patterns of release of the enzyme CK.

One difficulty in evaluating methods for measuring infarct size in man during life is that there is at present no absolute method against which other methods may be compared. In particular, discrepancies between infarct size assessed on the one hand by ST elevation, and on the other by total CK release, might be the result of deficiencies in the enzyme method rather than in the electrocardiographic mapping technique. Clearly, as has been discussed previously, these two variables are reflecting different pathophysiological processes; moreover it is possible that release curves of enzymes or products of myocardial catabolism other than CK might indicate a different duration or magnitude of myocardial necrosis. We have data on this point from an unpublished study in which the time course of release of CK was compared with that of α-hydroxybutyrate dehydrogenase (HBD) in a further 16 patients with transmural infarction. In 50 per cent of these patients the duration of release of the 2 enzymes was similar, while in 50 per cent HBD release continued for 11 to 48 hours after CK release had ended. Even if it is assumed that in these patients late HBD release represented continuing myocardial necrosis rather than hepatic damage from venous congestion, it is still likely that in many patients the duration of ST elevation was greater than that of myocardial necrosis as measured by HBD release.

From a practical viewpoint, a good correlation between total CK release and clinical indices of severity has been reported by ourselves (Norris *et al.*, 1975) and others (Sobel *et al.*, 1972; Mathey *et al.*, 1974). No comparable information is available from clinical studies of ST elevation, but a lack of correlation between clinical severity of infarct and praecordial ST elevation has already been suggested (Reese, Scheidt, and Killip, 1973). Thus, we believe that the measurement of CK release is an inherently more accurate method for the clinical assessment of myocardial infarct size than is the quantification of ST segment elevation.

A possible explanation for the present findings is that the extent of ST segment elevation overlying ischaemic myocardium is related only indirectly to the extent and degree of ischaemia, but more directly to mechanical or electrical imbalance occurring at boundaries between healthy and infarcting muscle. It is well known that paradoxical wall movement occurs at the site of an infarct, that this persists during the healing stage and even permanently if a ventricular aneurysm develops, and that this is associated with chronic ST segment elevation. Moreover, experimental evidence suggests that ST elevation is commonly greatest at boundaries between healthy and ischaemic tissue, and may diminish at the centre of large infarcts (Cohen and Kirk, 1974). Such an explanation for the causation of ST elevation would be consistent with the present finding that ST elevation often persists after myocardial necrosis has ceased, and declines gradually over 2 to 3 weeks as the infarct heals. It could also explain the effect of practolol, which caused a reduction in ST elevation at a time when necrosis was presumably complete. This effect could have occurred through reduction in paradoxical movement by beta-adrenergic receptor blockade at the boundary between infarcted and normal muscle. An alternative explanation for the reduction in ST elevation after practolol is that the change was related to slowing of the heart rate by the drug. However, the reduction in heart rate was slight (10%), and there was no relation between the degree of slowing in individual patients and the reduction in ST elevation; this finding is in agreement with that of Pelides *et al.* (1972) who found a similar degree of reduction in ST segment elevation after practolol (–19%, compared with –23% in the present study) in patients during the acute phase of myocardial infarction. The possibility that practolol reduced ST elevation by relieving persistent ischaemia, possibly at the boundary of the infarct, should also be considered, but seems unlikely, as the patients were fully convalescent and had been free of chest pain for several days before injection of the drug.

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Sinus node dysfunction in acute myocardial infarction

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The frequency, clinical course, and prognosis of sinus node dysfunction in 431 patients with acute myocardial infarction admitted to the coronary care unit were studied. Sinus node dysfunction occurred in 20 patients. In 13, the principal manifestation consisted of severe sinus bradycardia. In the remaining 7, periods of bradycardia alternating with episodes of supraventricular tachycardia were noted. Though several of the patients with sinus bradycardia required intravenous atropine or temporary pacing, normal sinus rhythm returned in virtually all during follow-up. The clinical course of patients with both bradycardia and tachycardia was less benign, during the acute phase and during follow-up; 5 of the 6 survivors required continued antiarrhythmic therapy or permanent pacing. The differences in the clinical course between these two groups of patients may reflect distinct underlying pathological changes. The findings in this study suggest that in contrast to sinus bradycardia, the occurrence of bradycardia-tachycardia syndrome during the acute phase of myocardial infarction may have important prognostic implications.

Sinus node dysfunction is being increasingly recognized as a cause of serious cardiac arrhythmias and frequently presents difficult problems in diagnosis and therapy. Characteristic manifestations of sinus node dysfunction include persistent bradycardia, episodes of brief or sustained sinus arrest, and the bradycardia-tachycardia syndrome (Ferrer, 1973; Rubenstein *et al.*, 1972). Previous clinical and clinicopathological studies have shown that all these manifestations of sinus node dysfunction may be seen during the acute phase of myocardial infarction (Rokseth and Hatle, 1971; Lippestad and Marton, 1967). However, little is known concerning the subsequent clinical course and prognosis of such patients. In the study reported here, the frequency, clinical course, and prognosis of sinus node dysfunction were analysed in 431 consecutive patients with acute myocardial infarction admitted to the coronary care unit.

Patients and methods

The charts and rhythm files of 431 consecutive admissions to the coronary care unit between January 1973 and July 1974 formed the material for this study. Since the admission policy to the coronary care unit in this institution dictates the exclusion of patients with severe congestive failure and cardiogenic shock, the patients included in this study were free from these major complications of myocardial infarction at the time of admission.

The cardiac rhythm of each patient was continuously monitored at a central console by trained technicians. A 40-s tape delay permitted the documentation of the onset and termination of any major change in the cardiac rhythm. At the end of each of the three 8-hour shifts, a summary of the arrhythmias, including representative rhythm strips, were incorporated into the patient's rhythm file. When arrhythmias requiring therapy with drugs occurred, the time, the dosage, and the route of administration of the drugs were also recorded.

Each chart and rhythm file was reviewed for evidence of sinus node dysfunction, which was considered to be present in patients with one or more of the following abnormalities: *(a)* persistent sinus bradycardia with rates less than 50 beats a minute during at least two consecutive 8-hour shifts; *(b)* sinoatrial block, 'sinus pause', or 'sinus arrest'; and *(c)* bradycardia-tachycardia syndrome. Patients in whom any one of the preceding arrhythmias was known to have been present before the myocardial infarction were excluded. Similarly, patients taking digitalis, propranolol, or reserpine were also excluded. Transient bradycardia associated with pain, or the administration of analgesic drugs was not considered evidence of sinus node dysfunction.

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In patients with sinus node dysfunction, the presence of acute myocardial infarction was confirmed using the usual criteria of a typical clinical history and sequential electrocardiographic and enzyme abnormalities. The presence of previous myocardial infarction was also noted. The time of onset of sinus node dysfunction, its duration, and the presence of associated arrhythmias were also recorded. The hospital charts were reviewed to obtain data during the hospital stay after discharge from the coronary care unit. Follow-up information was provided by the private physician from his records.

Results

Twenty patients fulfilled the criteria for sinus node dysfunction as set forth in the section on methods. There were 11 men and 9 women and their ages ranged from 39 to 79 years. Based on the major electrocardiographic manifestation during the acute phase, the 20 patients were subdivided into the following two categories: (a) those with severe sinus bradycardia, and (b) those with the bradycardia-tachycardia syndrome.

Sinus bradycardia

This group included 13 patients whose predominant clinical feature consisted of persistent sinus bradycardia with rates ranging between 30 and 50 beats a minute. Five patients also experienced brief episodes of supraventricular tachycardia lasting no longer than several seconds at a time. One patient was noted to have sinoatrial block. The average age of patients with sinus bradycardia was 69 years (range 42 to 79 years). The acute infarction was inferior in 11 and anterior in 2. A history of previous myocardial infarction was elicited in 5 patients. Sinus bradycardia was noted within 24 hours of admission in all patients and lasted from 24 hours to several days. In one patient, it lasted throughout the hospital course. Intravenous injections of atropine were used in all and resulted in a prompt but transient increase in the heart rate in 8. In 5 patients in whom atropine did not produce an increase in the heart rate, a proper evaluation of the effectiveness of the drug could not be made since the doses employed were small (0·4 mg). Two patients required temporary pacing. Significant associated arrhythmias consisted of. ventricular fibrillation in 1, ventricular tachycardia in 3, and atrioventricular block in 2. None of the patients developed congestive heart failure, and none died in hospital.

One patient was lost to follow-up, and another died from recurrent myocardial infarction five months after discharge. In the remaining 11 patients, clinical data and electrocardiograms were available for periods ranging between 10 and 30 months after discharge. Ten patients have had no bradycardia or any of the other manifestations of sinus node dysfunction. One patient, who was noted to have episodes of sinoatrial block during the acute phase of myocardial infarction, has continued to have sinus bradycardia though he remains asymptomatic (Fig. 1).

Bradycardia-tachycardia syndrome

Of the 7 patients in this group, 4 had inferior infarcts, 2 had anterior infarcts, and the remaining patient had a non-transmural infarct. Their ages ranged between 39 and 77 years, with an average of 70 years. None gave a history of previous myocardial infarction. The clinical course in these 7 patients was characterized by prolonged episodes of atrial tachyarrhythmias alternating with periods of sinus bradycardia and slow escape rhythms. One patient, who was admitted with sinus bradycardia, developed atrial fibrillation shortly after admission and, within a few hours, developed ventricular standstill which did not respond to attempts at resuscitation. In 5 of the 6 remaining patients, tachyarryhthmias became manifest within 24 hours of admission and lasted throughout the period of hospital stay. In 1 patient, episodes of tachyarrhythmias subsided within 48 hours of admission. The tachycardias were variable in duration, lasting from a few seconds to several hours. Spontaneous cessation of tachycardias was followed by prolonged periods of sinus standstill (Fig. 2) requiring the insertion of temporary pacemakers in 5 patients. Though radiological evidence of mild left ventricular failure was observed in many during tachycardia, none developed significant congestive failure or hypotension.

Five of the 6 survivors in this group have continued to experience recurrent episodes of atrial tachycardia, flutter, or fibrillation during the 30-month follow-up period. Four have required permanent pacing in addition to a combination of antiarrhythmic drugs, and one has remained well on antiarrhythmic drugs alone. The only patient who has required neither drugs nor a permanent pacemaker was the one noted to have tachycardias only for a 48-hour period during the acute phase of infarction. Thus, in contrast to the patients with sinus bradycardia, the occurrence of bradycardia-tachycardia syndrome during the acute phase was associated with persistence of this arrhythmia during follow-up.

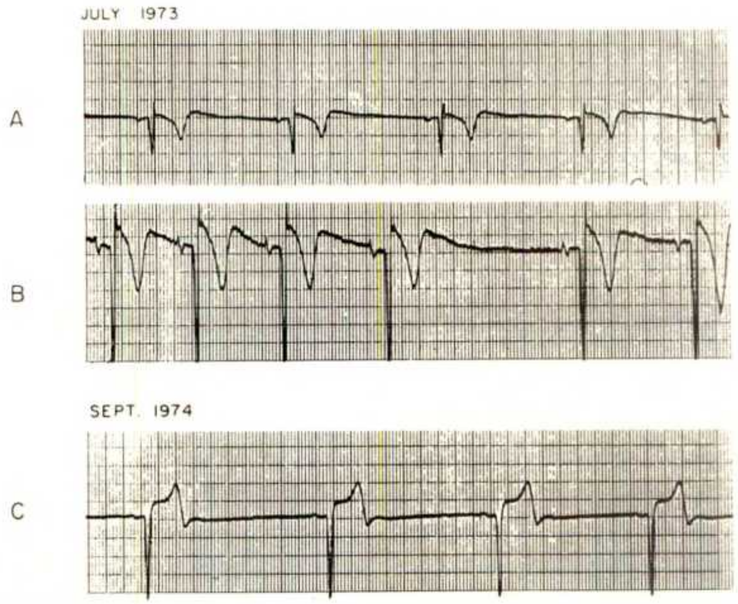

FIG. 1 *Representative rhythm strips from a patient with acute inferior myocardial infarction and persistent sinus bradycardia. Panels A and B were recorded during the acute phase and show severe sinus bradycardia (A), and episodes of sinoatrial block (B). Severe sinus bradycardia has persisted during repeated follow-up examinations (panel C) though the patient remains asymptomatic (see text for discussion).*

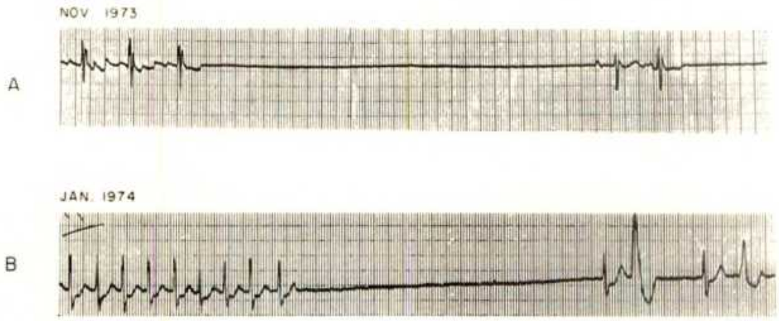

FIG. 2 *Rhythm strips from a patient with inferior myocardial infarction and bradycardia-tachycardia syndrome. The top strip (A) was recorded 3 days after myocardial infarction, and the bottom strip (B), upon readmission 2 months later. Note periods of prolonged sinus standstill after cessation of the tachycardia.*

Discussion

Previous studies have reported an incidence of between 4 and 5 per cent for sinus node dysfunction in patients with acute myocardial infarction (Rokseth and Hatle, 1971; Rotman, Wagner, and Wallace, 1972). In the present study, sinus node dysfunction was noted in 20 out of 431 patients with acute myocardial infarction, yielding an incidence of 4·6 per cent. Though the exclusion of patients with congestive failure and cardiogenic shock may have eliminated some additional patients with sinus node dysfunction, it must be kept in mind that the drugs used in the therapy of both these complications may give rise to arrhythmias of the type described, making the diagnosis of sinus node dysfunction difficult.

Analysis of the clinical data revealed no relation between sinus node dysfunction and the age, sex, or a history of previous myocardial infarction. There was a preponderance of inferior infarction in the group as a whole. This relation was particularly striking in the case of sinus bradycardia, whereas in patients with bradycardia-tachycardia syndrome, the proportion of inferior to anterior infarcts was similar to that observed by James (1961) in a group with atrial arrhythmias. There appeared to be no relation between sinus node dysfunction and the severity of myocardial infarction as judged by the mortality or the subsequent development of congestive heart failure or hypotension. This is in contrast to the high incidence of such complications reported by Rokseth and Hatle (1971). Though the reasons for this difference are unclear, it is possible that the early use of temporary pacing in our patients played a role in preventing such complications.

The most interesting observation in this study concerned the dissimilarity in the subsequent clinical course between patients presenting with sinus bradycardia and those with the bradycardia-tachycardia syndrome. It is notable that 5 out of 7 patients with the latter arrhythmia required permanent pacing in addition to antiarrhythmic drugs, whereas none of the patients with sinus bradycardia alone required such measures. This difference may be explained by the differences in the underlying pathology and pathogenesis between these two types of arrhythmias after acute myocardial infarction. During the acute phase of myocardial infarction sinus bradycardia may be caused by a variety of factors including pain, fear, the administration of analgesic drugs, or depression of sinus node automatically induced by ischaemia, cholinergic influences, and products of tissue breakdown (Rotman *et al.*, 1972; Billette *et al.*, 1973). Though the criteria used in the selection of patients in this study excluded those with transient bradycardia as a result of pain, fear, and drugs, the onset and duration of the arrhythmia in most instances were compatible with vagally mediated depression of the sinus node. In patients with the bradycardia-tachycardia syndrome on the other hand, pathological studies have shown characteristic lesions consisting of infarction of the sinus node and the adjacent atrium (Lippestad and Marton, 1967; James, 1961). As suggested by James (1961), such a combination of sinus node and atrial damage appears to provide an explanation for the occurrence of the bradycardia-tachycardia syndrome during the acute phase and its persistence after recovery. The atrial damage, by virtue of its proximity to the sinus node, may impair conduction from the sinus node and also predispose to re-entry and re-entrant tachycardias. Since the impairment of sinoatrial conduction may be expected to persist after healing of the infarction, the arrhythmia may recur after recovery from the acute infarct.

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Significance of serum enzyme changes after cardiac catheterization and selective coronary arteriography

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The serum creatine kinase (CK), aspartate transaminase (AST), lactic dehydrogenase (LD) and α-hydroxybutyric dehydrogenase (HBD) were determined before and 3, 6, 18, and 36 hours after cardiac catheterization and angiocardiography in 56 consecutive patients with ischaemic heart disease. Five of these patients whose serum enzyme levels were higher than normal before the procedure were excluded from the study. Forty-one of the remaining 51 patients had left ventriculography and also selective coronary arteriography. In these 41 patients (groups 1 and 2—see below), the mean serum CK levels increased after the procedure to exceed the upper limit of normal at every study interval. The mean serum AST, LD, and HBD levels generally remained within the normal range at all study intervals, though serum AST increased abnormally in 9 of the 41 patients (22%) and serum LD and HBD each increased above the normal limit in 2 of 41 patients (4·9%).

In 24 patients (group 1) whose coronary arteriograms showed insignificant coronary narrowing (< 75%) in any of the three major coronary arteries, the increase in serum CK was significantly higher than in 17 patients (group 2) with greater than 75 per cent narrowings in at least one of the three major coronary arteries. However, the degree of serum CK elevation observed during the postangiographic period was much lower than that in another group of 30 consecutive patients with acute myocardial infarction. In 10 *patients (group* 3*) who had the same procedure as groups* 1 *and* 2 *except without the selective coronary arteriography, the serum enzyme levels showed no noticeable increase after the procedure.*

The difference in postangiographic serum CK elevation between patients with and without selective coronary arteriography and the difference between group 1 *(without significant coronory narrowing) and group* 2 *(with significant narrowing) strongly suggest that the raised serum CK levels represent some form of myocardial damage caused by the coronary arteriography, which, however, is different at least in degree from that of acute myocardial infarction.*

Serum enzyme changes after cardiac catheterization and coronary arteriography play an important role in the clinical diagnosis of complicating myocardial infarction. However, controversy still exists as to the usual extent and the significance of these changes. Taquini *et al.* (1961) noted that serum transaminase (AST) levels were raised after transseptal left heart catheterization, and Adrouny *et al.* (1963) also noted the increase in serum AST in a significant number of subjects undergoing cardiac catheterization and angiography, whereas others found no significant changes (Kochsiek and Engelhardt, 1965; Burkhardt *et al.*, 1968). Serum creatine kinase (CK) has been reported in many studies to increase after cardiac catheterization and/or angiocardiography (Marpole *et al.*, 1968; Michie *et al.*, 1970), while no noticeable changes in serum lactic dehydrogenase (LD) and α-hydroxybutyric dehydrogenase (HBD) were reported by Sitzmann and Gutheil (1966). These discrepancies may be caused by differences in the kind of cardiac disease and/or the procedures undertaken in these studies.

However, few studies have reported the serum enzyme changes after coronary arteriography (Michie *et al.*, 1970; Chahine, Eber, and Kattus,

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1974), and there are no reports of investigations of the relation between the severity of coronary narrowing and the extent of serum enzyme changes after coronary arteriography. In this study in patients with ischaemic heart disease, serum CK, AST, LD, and HBD levels were determined before and after cardiac catheterization (left ventriculography with or without selective coronary arteriography) to investigate the correlation between coronary narrowing and the extent of serum enzyme increase.

Subjects and methods

The serum levels of CK, AST, LD, and HBD were measured before and 3, 6, 18, and 36 hours after cardiac catheterization and angiocardiography in 56 consecutive patients with ischaemic heart disease. Five patients with abnormal serum enzyme levels before the procedure were excluded from the study. Of the remaining 51 patients, 41 patients (groups 1 and 2—see below) had cardiac catheterization, left ventriculography, and selective coronary arteriography without a major complication, while in 10 patients (group 3 as a control group) selective coronary arteriography was avoided because of complications such as arrhythmia and/or heart failure. One patient in group 3 complained of chest pain during the procedure. In the 41 patients of groups 1 and 2, no subjects had any clinical evidence of liver disease, skeletal muscle disease, pericarditis in the acute stage, or congestive heart failure during the study.

The 41 patients undergoing selective coronary arteriography were divided into two groups. Group 1 consisted of 24 patients (aged 43 to 66 years, average 50·3 years) whose coronary arteriograms showed less than 75 per cent narrowings in any of the three major coronary arteries. All of them showed minor obstructive lesions in one or two major caronary arteries except one patient with a variant form of angina who had no narrowing in any of the three vessels. This group consisted of 11 patients with a previous myocardial infarct (6 weeks to 2 years previously) and 13 patients with angina pectoris (8 patients with effort angina, 3 patients with variant form of angina, 1 patient with rest angina, and 1 patient with effort angina combined with variant form of angina). Group 2 consisted of 17 patients (aged 54 to 70 years, average 58·1 years) whose coronary arteriograms showed significant narrowings (>75%) at least in one of the three major coronary arteries. This group consisted of 14 patients with previous myocardial infarction and 3 patients with angina pectoris (2 patients with effort angina and 1 with a combination of effort, rest, and variant form of angina).

Group 3 consisted of 10 patients undergoing cardiac catheterization and left ventriculography but without selective coronary arteriography. The age of the patients in this group ranged from 38 to 60 (average 52·2 years). There were 4 patients with previous myocardial infarction, 4 patients with angina pectoris (2 patients with effort and rest angina, 2 with variant form of angina), and 2 with atypical chest pain.

The previous myocardial infarctions were diagnosed by clinical history and electrocardiographic examination before the catheterization and, in some cases, the diagnosis had been confirmed by serum enzyme increases in the acute stage. Effort angina was diagnosed with the ergometer exercise test and the diagnosis of rest and variant form of angina was made on the basis of typical chest pain and the electrocardiographic changes during an attack.

Left ventriculography, using 40–50 ml contrast medium (Urografin 76: sodium diatrizoate) was performed in all patients after premedication using oral diazepam (10 mg) and intramuscular atropine sulphate (0·5 mg) and hydroxyzine (50 mg). Selective coronary arteriography was performed using a total of 30 to 40 ml of the same contrast medium given by four manual injections. The transfemoral percutaneous approach was used for right and left heart catheterization and angiography. Nitroglycerin (0 3 mg) was administered sublingually just before the selective coronary arteriography was done. The cardiac output was determined by the dye-dilution technique in all patients (groups 1, 2, and 3).

The enzyme assays were performed either immediately after sampling or within 15 hours after separation of serum (stored at 4°C). The normal values and determination method of serum enzyme levels in our laboratory are: for CK (less than 40 IU) method of Nuttall-Wedin (Nuttall and Wedin, 1966); for AST (0 to 40 units) modified method of Reitman-Frankel (Reitman and Frankel, 1957); for LD (30 to 140 units) method of Naclas (Naclas *et al.*, 1960) and for HBD (40 to 170 units) modified method of Rosalki (Rosalki and Wilkinson, 1960).

As a comparative study, 30 consecutive patients with acute myocardial infarction were studied. In this group, serum levels of CK, AST, LD, and HBD were determined 6, 18, and 36 hours after the onset of chest pain.

Statistical evaluation of the data was done by applying Student's t-test.

Results

Table 1 shows the serum enzyme levels before and after cardiac catheterization and left ventriculography with or without selective coronary arteriography in 51 patients (groups 1, 2 and 3). The serum enzyme changes in 41 patients (groups 1 and 2) who had selective coronary arteriography are illustrated in Fig. 1. In the 41 patients, the mean serum CK levels significantly increased 3, 6, 18, and 36 hours after the procedure ($P < 0{\cdot}001$) with the maximal mean value of 48·1±4·1 IU which was 3·5 times higher than the mean value before the procedure, occurring 6 hours after the conclusion of coronary arteriography. The mean serum AST levels increased from 25·0±0·9 units to 30·2±1·3 units and 31·4±1·8 units at 3 and 6 hours after the procedure, respectively. Though these serum AST increases were statistically significant ($P < 0{\cdot}01$), they remained within the normal range. As to individual variations, serum

TABLE 1 *Serum enzyme levels (mean ±SE) before and after cardiac catheterization, left ventriculography with or without selective coronary arteriography in groups 1, 2, and 3*

Group 1 (n = 24)

Serum enzyme	*Before catheterization*	*After coronary arteriography*			
		3 *hrs*	6 *hrs*	18 *hrs*	36 *hrs*
CK	14·9±1·9	58·6±10·0**	64·1±6·5**	58·3±6·0**	52·8±5·6**
AST	26·1±1·3	31·5±1·7	32·3±1·8*	28·9±1·8	30 8±2·4
LD	88·8±3·0	97·3±3·9	97·5±4·5	87·4±3·9	86·8±3·5
HBD	94·0±4·9	109·4±5·0	116·5±4·2*	100·3±4·4	88·8±3·8

Group 2 (n = 17)

Serum enzyme	*Before catheterization*	*After coronary arteriography*			
		3 *hrs*	6 *hrs*	18 *hrs*	36 *hrs*
CK	11·8±1·6	20·4±2·4*	25·5±3·8*	21·9±4·2*	19 7±2·9*
AST	23·5±1·1	28·4±3·0	30·1±3·6	22·5±3·0	26·8±3·1
LD	89·1±4·1	95·6±5·0	96 5±4·0	95·5±8 1	97·0±7·5
HBD	117·1±7·3	119·1±8·0	125·0±9·6	135 5±19 7	119·6±15 0

Group 3 (n = 10)

Serum enzyme	*Before catheterization*	*After left ventriculography*			
		3 *hrs*	6 *hrs*	18 *hrs*	36 *hrs*
CK	11·3±2·2	18·1±3·5	19·2±4·2	18·4±3·7	22 2±3·4*
AST	22·2±2·1	23·9±1·9	28 8±1·7	23·4±2·4	22·8±1·7
LD	95·4±4·6	99·6±4·2	104·0±5·6	100·8±5·4	93·2±5·2
HBD	101·0±6·8	114·0±8·5	115·5±10·2	106·0±9·4	103·5±7·8

*Significantly different from the preangiographic value (P<0·01)
**Significantly different from the preangiographic value (P<0·001)

AST levels slightly exceeded the normal limit in 9 of 41 patients (22%).

The mean serum LD and HBD levels did not show a significant increase at any study interval during the postangiographic period, with the exception of the serum HBD at 6 hours after the procedure, which was still within the normal range. Incidence of an abnormal increase in individuals in serum LD and HBD after the procedure was 4·9 per cent (2 of 41 patients) each. There was only one patient who showed an abnormal increase in both serum LD and HBD.

In 10 patients in group 3 who had the same procedure but without selective coronary arteriography, no serum enzyme levels showed abnormal increase, though the mean serum CK and AST levels increased slightly after the procedure (see Table 1).

In group 1 (the 24 patients with insignificant coronary narrowings) the serum CK levels increased significantly at every study interval after angiography (P<0·001), with every mean value being much higher than the normal upper limit (see Fig. 2).

In group 2 (the 17 patients with significant coronary narrowing) in contrast to group 1, the serum CK levels were increased much less and in fact were much closer to the CK levels in the control group 3. The maximal mean value was observed 6 hours after the procedure in both groups: 64·1±6·5 IU in group 1 and 25·5±3·8 IU in group 2. In group 3 (the 10 patients without selective coronary arteriography) the mean serum CK levels increased significantly only at 36 hours (22·2±3·4 IU, P<0·01) but was still within the normal limit. There was no significant difference in serum CK levels between groups 2 and 3 at any study interval (see Fig. 2). In contrast to this, a significant difference (P<0·001) in the postangiographic serum CK levels was noted at every

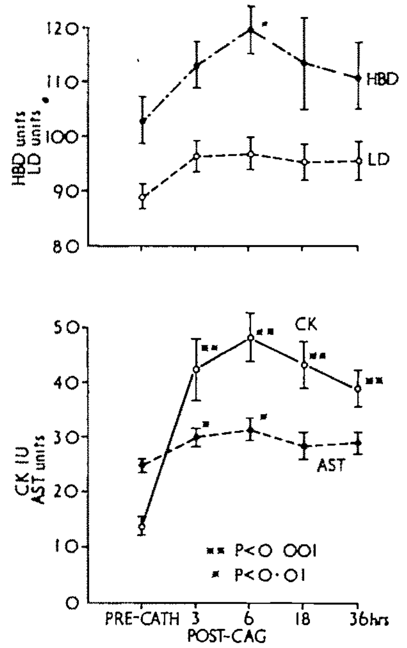

FIG. 1 *Changes in serum enzyme levels (mean ± SE) in 41 patients with ischaemic heart disease before cardiac catheterization (Pre-cath), and after (Post-cag) left ventriculography and selective coronary arteriography.*

**Significantly different from the preangiographic value (P < 0·01)*

***Significantly different from the preangiographic value (P < 0·001)*

study interval between groups 1 and 2, while the preangiographic values showed no significant difference between these two groups. A more remarkable difference was obtained when the patients with previous myocardial infarction from both groups were compared (11 patients in group 1 and 14 patients in group 2, see Fig. 3). The maximal mean value of serum CK obtained 6 hours after the procedure was 86·8±8·9 IU in these patients in group 1, but only 27·5±4·4 IU in group 2. The time from the onset of infarction to the angiographic examination showed no significant difference between the patients of these groups with previous myocardial infarction. There was also a difference in CK levels at 6 hours after the procedure between groups 1 and 2 in the patients with angina pectoris (13 patients in group 1, 3 in group 2), and the Student's t-test (P < 0·02) suggests that it is significant. The mean serum AST levels increased slightly in group 1 (P < 0·01), but the maximal mean values in groups 1 and 2, which were both within the normal range, showed no significant difference between these two groups (Fig. 4). The mean serum LD levels showed insignificant fluctuations within normal limits after the procedure. No significant difference was noted between the preangiographic and postangiographic mean HBD levels except for the mean value after 6 hours in group 1 (P < 0·01).

As a comparative study, the serum CK, AST, LD, and HBD were determined 6, 18, and 36 hours after the onset of chest pain in 30 consecutive patients with acute myocardial infarction. Table 2 shows the mean values of the various serum enzymes after the onset of infarction. All serum enzymes increased distinctly in acute myocardial infarction in comparison with those in the patients undergoing cardiac catheterization and angiography, though there was some individual overlap between the post-coronary arteriographic group (groups 1 and 2) and this control group. No individual overlap was observed between these groups in the serum LD and HBD levels at 18 and 36 hours.

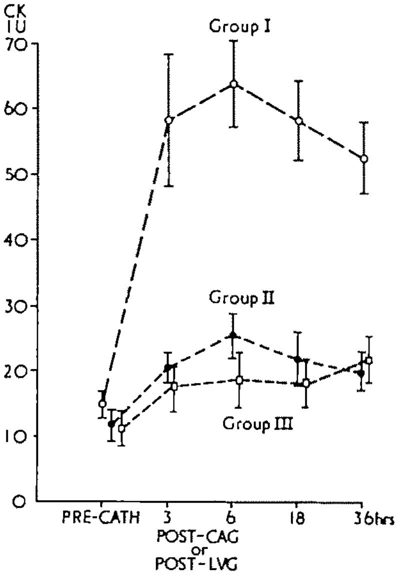

FIG. 2 *Postangiographic serum CK levels (mean ± SE) in groups 1, 2, and 3. Between groups 1 and 2, significant difference (P < 0·001) in the serum CK levels was noted at every study interval after the procedure, while no significant difference was observed between groups 2 and 3.*

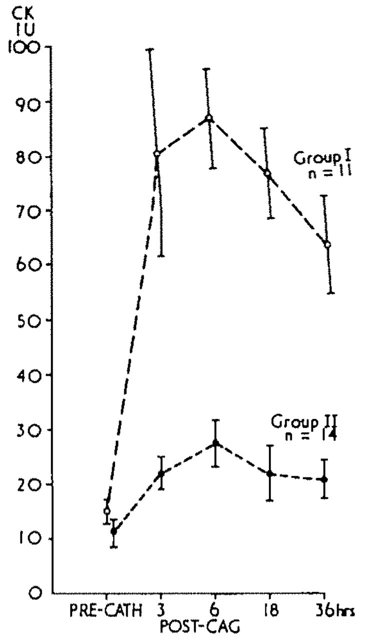

FIG. 3 *Postangiographic serum CK levels (mean ± SE) in patients of groups 1 and 2 with previous myocardial infarction. A distinct difference ($P < 0{\cdot}001$) was observed between these two groups at every study interval.*

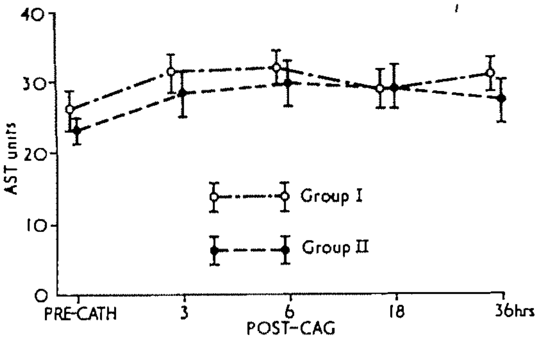

FIG. 4 *Serum AST levels (mean ± SE) of 41 patients with ischaemic heart disease in groups* 1 *and* 2. *No significant difference was observed between these two groups at any study intervals.*

Discussion

Serum enzyme changes were studied in 41 patients with ischaemic heart disease before and after cardiac catheterization, left ventriculography and selective coronary arteriography, and in 10 patients after cardiac catheterization and left ventriculography but no selective coronary arteriography. A pronounced increase in the postangiographic serum CK levels was observed in the patients with insignificant coronary narrowings (group 1), while the serum CK levels in the patients with greater than 75 per cent coronary narrowings (group 2) and those without selective coronary arteriography (group 3) showed only a slight increase within the normal range. In contrast to CK, the mean values of other serum enzymes—AST, LD, and HBD, showed minimal fluctuations within normal limits in all these groups. The significant difference in postangiographic serum CK levels between group 1 and groups 2 and 3 suggests that the raised serum CK levels could be attributed to the myocardial response to the injection of contrast medium and may reflect underlying myocardial conditions.

TABLE 2 *Serum enzyme levels (mean ± SE) in 30 consecutive patients with acute myocardial infarction*

Serum enzyme	*Hours after onset of infarction*		
	6 hrs	*18 hrs*	*36 hrs*
CK	70·5±11·3	244·3±26·8	238·2±33·9
AST	49·5±4·7	154·7±13·9	175·6±21·1
LD	129·3±11·2	302·1±41·7	461·0±63·6
HBD	178·8±13·9	484·2±51·0	784·3±84·0

The significance and extent of the changes in serum enzymes after coronary arteriography have been studied extensively (Michie *et al.*, 1970; Chahine *et al.*, 1974), whereas those after cardiac catheterization and/or angiography, which have been reported by many authors, are often conflicting. For instance, Adrouny *et al.* (1963) reported that the serum AST exceeded the normal limit in 55 per cent of the subjects undergoing cardiac catheterization and in 33 per cent of the subjects who received angiocardiography, while Burkhardt *et al.* (1968) described no significant rise in serum AST in 113 patients using a similar procedure and significant increases in serum LD and HBD in only a few cases. These discrepancies could be due to the difference in the conditions of the study. Premedication, procedures of angiography, and the intervals of time the subjects were studied after the procedure were different in these different reports.

We determined the serum enzyme levels before and 3, 6, 18, and 36 hours after cardiac catheterization, left ventriculography, and selective coronary arteriography in 41 patients with ischaemic heart disease. In our study, no significant increase was seen in serum LD and HBD except for minimal increase in serum LD in 2 of 41 patients (4·9%) and in serum HBD also in 2 patients. The mean serum AST levels remained within the normal range at all study intervals, though the individual values slightly exceeded the normal upper limit in 9 of 41 patients (22%). Chahine *et al.* (1974) described abnormal rises in serum AST in only 2 per cent of patients 24 hours after the cardiac catheterization and coronary arteriography. Our data, which showed the maximal increase at 6 hours after the procedure, suggests that they may have failed to detect the early rise in serum AST.

In our study, all 41 subjects received the same premedication and the same angiographic procedure including the approach of catheterization, and the type and amount of contrast medium. However, a much greater rise in serum CK during the post-angiographic period was observed in the patients without significant coronary narrowings rather than in those with. When 25 patients of groups 1 and 2 with previous myocardial infarction were compared, an even more remarkable difference was observed in the CK rises between the 11 patients with significant coronary narrowings and the 14 patients without. The same tendency (i.e. less narrowing, the higher the rise in CK) was seen among 16 patients with angina pectoris, though there were only three angina patients in group 2. We observed no noticeable increase in serum CK levels in 10 patients with ischaemic heart disease who received the same procedure with the same premedication except that selective coronary arteriography was avoided because of complications such as arrhythmia and/or heart failure.

These findings suggest that most of the increase in serum CK is of cardiac origin, and that the extra-cardiac factors such as the local tissue trauma at the site of introduction of the catheter and intramuscular premedication (as previously suggested by Crowley (1968) and Chahine *et al.* (1974)) contribute only minimally, if at all. The magnitude of serum CK rise during the postangiographic period, however, was much lower than that in the patients with acute myocardial infarction, though some overlap was seen between these two groups in the range of individual variations. In contrast to CK, coronary arteriography did not produce a significant rise in the serum LD and HBD levels. This may indicate that the myocardial damage caused by coronary arteriography is from a different mechanism than that of acute myocardial infarction. Wexler (1970) noted that serum CK is a sensitive index of not only myocardial necrosis but also of sarcolemmal membrane permeability. Whether the increase in serum CK after coronary arteriography is caused by transient ischaemia or by alteration of membrane permeability could not be determined from this study.

It is surprising that the serum CK increased in the patients without significant coronary narrowings (group 1), but not in the patients with significant coronary obstructions (group 2). This paradoxical observation may suggest either poor perfusion of contrast medium and/or a decreased number of myocardial cells which contribute to CK release in the patients with severe coronary narrowings. Hyperaemic response after intracoronary injection of contrast medium may also contribute to the release of CK from the myocardium. This speculation assumes additional interest in view of the report by Gould and Lipscomb (1974) of distinct hyperaemic response to contrast medium in coronary arteries without severe narrowings. Further investigations are necessary to clarify the mechanism by which CK is released from ischaemic myocardium after coronary arteriography.

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Case reports

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Spasm of left main coronary artery

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A 46-year-old male patient with atypical angina pectoris appeared to have an important elongated stenosis of the left main coronary artery on coronary arteriography, and slight irregularities in the left anterior descending, circumflex, and right coronary arteries. A saphenous vein bypass graft to the left anterior descending artery was performed, and this relieved the patient's symptoms. Postoperative coronary arteriography demonstrated a widely patent left main coronary artery and graft. The original narrowing of the left main coronary artery was probably caused by spasm and the source of the patient's anginal symptom.

Coronary artery spasm has been proven experimentally in animals (Gensini *et al.*, 1962) and angiographically in patients with angina pectoris (Oliva, Potts, and Pluss, 1973; Dhurandhar *et al.*, 1972). It is probably an important factor in variant angina pectoris (Prinzmetal *et al.*, 1959; MacAlpin, Kattus, and Alvaro, 1973) and may be a precipitating factor in acute myocardial infarction. Spasm may occur in patients with normal coronary arteries (King *et al.*, 1973) and may be the cause of myocardial infarction, arrhythmias, and possibly sudden death.

Previous reports have described spasm of the right coronary artery (Oliva *et al.*, 1973; O'Reilly, Spellberg, and King, 1970). In contrast, we describe a patient with spasm leading to narrowing of the left main coronary artery which we suspected to be caused by an organic lesion. He underwent saphenous vein bypass graft implantation, but subsequent angiographic examination showed a patent, normal left main coronary artery.

Case report

A 46-year-old bus driver was admitted for coronary arteriography. A year before admission he complained of praecordial pain which radiated to the left shoulder and was not clearly related to effort. He was admitted to hospital twice with severe chest pain with transient T wave inversion in the praecordial leads, but without signs of acute myocardial infarction. He had mild diabetes mellitus (fasting blood glucose level of 130 mg/100 ml (7.2 mmol/l)), type 4 hyperlipidaemia (serum triglyceride 400 mg/100 ml (4.5 mmol/l), cholesterol 300 mg/100 ml (7.8 mmol/l)), and smoked 60 cigarettes a day.

Physical examination was non-contributory. Blood pressure: 135/90 mmHg (18.0/12.0 kPa). There were no signs of heart failure, the heart was not enlarged, and the heart sounds were normal. Electrocardiogram showed sinus rhythm at a rate of 100 a minute, and flat T waves in the praecordial leads. The chest *x*-ray was normal.

Selective coronary arteriography was performed using the Judkins' technique (Judkins, 1967; Gotsman *et al.*, 1973) with premedication of diazepam 10 mg and pethidine 50 mg. Atropine was not given because of sinus tachycardia: nor was sublingual isosorbide dinitrate given. A 4 cm Judkins left coronary catheter was introduced first. The left coronary artery ostium was intubated repeatedly but in each instance blood pressure fell: the tip of the catheter was withdrawn promptly. After several entries into the ostium, the blood pressure did not change and blood could be aspirated freely from the catheter. An injection of 3 ml Renografin 76 was made, and screening suggested obstruction of the left main coronary artery immediately beyond its origin: the catheter was withdrawn immediately. The arterial pressure fell slowly and severe bradycardia occurred: this did not respond to 2 mg intravenous atropine, the patient lost consciousness, and the electrocardiogram showed cardiac standstill. Cardiac resuscitation was successful, the patient regained consciousness, blood pressure returned to normal, and the electrocardiogram returned to its previous pattern.

The patient was allowed to recover for 90 minutes. A temporary pacemaker was inserted with its tip at the apex of the right ventricle and further selective injections were made into the right coronary artery. Each injection was followed by a fall in blood pressure and severe T wave inversion.

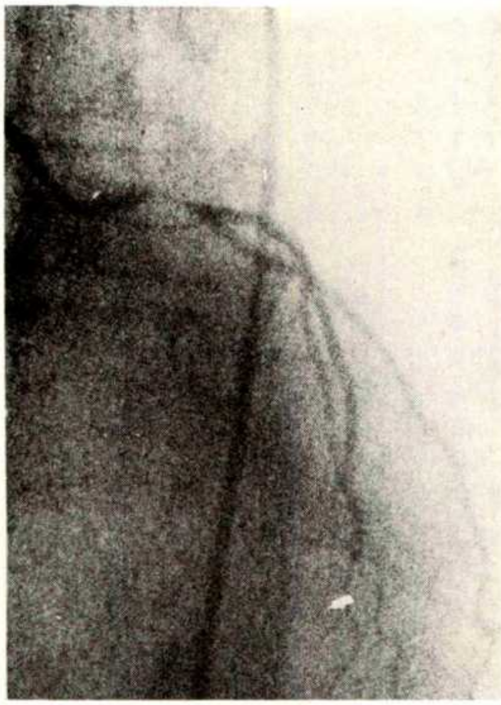

FIG. 1 *Preoperative, selective left coronary arteriogram (AP position) shows severe elongated narrowing of the middle two-thirds of the main left coronary artery. The remainder of the artery and its branches show slight irregularities.*

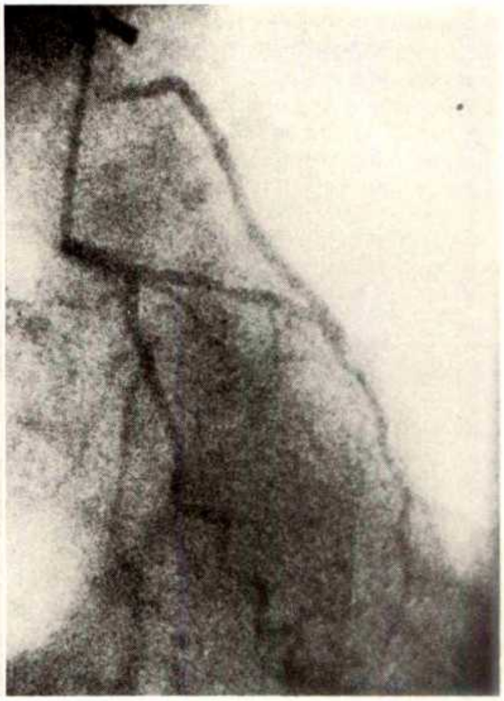

FIG. 2 *Selective left coronary arteriogram after saphenous vein bypass grafting (30° right anterior oblique position). The left main coronary artery is small and the venous bypass graft fills retrogradely. There are small areas of atheromatous narrowing of the left anterior descending artery, with an important stenosis in its proximal third. The vessels are tortuous.*

The cineangiogram showed a 95 per cent obstruction affecting a long segment of the left main coronary artery (Fig. 1): the left anterior descending and circumflex arteries and their branches showed slight irregularities. The right coronary artery was normal and no collateral filling of the left coronary system was observed. Because of the potentially lethal nature of the suspected left main coronary obstruction and the clinical reaction to left coronary angiography, further selective injections into the left artery were not made and it was decided to submit the patient to immediate operation. Several observers doubted the organic nature of the obstruction since the other vessels did not show major obstructions and collateral vessels from the right coronary artery were not seen. The possibility of spasm of the artery or dissection of the intima were suggested.

At operation no gross atheromatous lesions could be palpated. Upon incision of the left anterior descending artery excellent forward flow of blood was noticed. Nevertheless, a reversed saphenous vein bypass graft was inserted between the aorta and the proximal third of the left anterior descending artery. The flow through the graft was 60 ml/min.

The postoperative course was uneventful. The chest pain disappeared.

Four weeks later coronary arteriography was repeated. On this occasion 5 mg sublingual isosorbide dinitrate was given before arteriography. Selective injections of Renografin were made into the venous graft, and into the right and left coronary arteries in several different projections: these showed a patent graft, a long and widely patent left main coronary artery, with atheroma in the left anterior descending artery (Fig. 2), and a normal right coronary artery. There was no change in blood pressure during injection into the venous graft or left coronary artery: during right coronary injection, a fall in blood pressure occurred and was accompanied by T wave inversion.

Discussion

Prinzmetal *et al.* (1959) proposed spasm of a coronary artery as a cause for a characteristic anginal syndrome, associated with chest pain appearing at rest, accompanied by ST segment elevation, and a stable electrocardiogram between attacks. Most of the patients had pre-existing atheromatous narrowing of one or more of the proximal major coronary arteries. Coronary spasm was blamed as the trigger factor. Several other reports of Prinzmetal variant angina have appeared and a few patients had severe ST segment elevation on the electrocardiogram despite normal coronary arteries proven at coronary arteriography (O'Reilly *et al.*, 1970; Whitting *et al.*, 1970; Silverman and Flamm, 1971; Demany, Tambe, and Zimmerman, 1968). In a patient with variant angina pectoris spasm of the right coronary artery during an attack has been demonstrated angiographically (Oliva *et al.*, 1973; Dhurandhar *et al.*, 1972). Spasm of the coronary arteries may also occur after withdrawal of nitroglycerin in patients in whom chronic exposure has caused persistent vasodilatation (Lange *et al.*, 1972). There is good evidence, therefore, that coronary spasm, though uncommon, does occur.

Our patient suffered from severe episodes of chest pain, thought to be caused by inadequate coronary blood flow, and was admitted to hospital twice for severe praecordial pain with T wave inversion. He had many coronary risk factors: mild diabetes mellitus, type 4 hyperlipidaemia, and a history of heavy smoking. At coronary angiography he appeared to have severe stenosis of the left main coronary artery, developed cardiac standstill, lost consciousness, and required resuscitation: a diagnosis of left main coronary obstruction was made and further injections into the left coronary artery were not performed because of the possible risk to life. The severe T wave changes which appeared during injection of contrast medium into the right coronary artery, which were accompanied by a transient fall in blood pressure, supported the suggestion of coronary artery obstruction. However, demonstration of a widely patent left main coronary artery a month after the operation, confirmed a preoperative suspicion that this was caused by spasm of the artery.

The cause of the coronary arterial spasm in this patient is uncertain: it may have been caused by mechanical irritation by the tip of the catheter, a result of injection of the contrast medium (Gensini *et al.*, 1962; O'Reilly *et al.*, 1970; Meaney and Buonocore, 1966; Wickbom and Bartley, 1957), or a consequence of an independent phenomenon responsible for the anginal syndrome. A mechanical factor or subintimal dissection cannot be excluded. The last two are unlikely since antecedent chest pain at home was accompanied by T wave changes, and similar changes appeared during the right coronary angiogram. The postoperative improvement in the clinical syndrome is difficult to explain: it may be a placebo effect or a real improvement in left coronary blood flow during spasm. MacAlpin *et al.* (1973) and King *et al.* (1973) treated patients with variant angina pectoris by saphenous vein bypass grafts and had a high mortality and a low rate of improvement: they considered associated spasm of the vessel distal to the graft as the cause for lack of improvement.

The right coronary artery is more frequently involved in spasm (MacAlpin *et al.*, 1973; Aisner, 1970; Kemp *et al.*, 1973), and most reports on variant angina pectoris demonstrate ST elevation in the inferior leads (II, III, aVF), indicating involvement of the right coronary artery. Some believe this to be caused by a sphincter-like muscle at the orifice of the artery (Boucek, Takeshita, and Brady, 1965). Our patient is the first in whom left main coronary artery spasm has been reported. We remain uncertain whether spasm of the left main coronary artery has the same grave prognosis reputed to be associated with atheromatous narrowing of it. Severe spasm, however, may be a cause of angina pectoris (as in this patient), acute myocardial infarction, and even sudden death in the presence of normal coronary arteries (MacAlpin, 1973; Carmichael and Lieben, 1963).

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Cor triatriatum dexter with imperforate Ebstein's anomaly

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A case of cor triatriatum dexter is described in which the anomalous right atrial partition is identified as the right venous valve; there is an associated anomaly of the right atrioventricular valve which combines features of Ebstein's anomaly, and an atypical, imperforate, tricuspid atresia.

Subdivision of the right atrial cavity into two chambers is a rare cardiac anomaly; to the best of our knowledge only 16 cases have been described previously.

Doucette and Knoblich (1963) reviewed 8 published cases and added a further example; Kauffman and Andersen (1963) found reference to 2 additional reported cases and also added a further personal case; and Jones and Niles (1968) and Runcie (1968) each reported single cases. The condition is generally identified at necropsy but a clinically diagnosed case was described by Verel, Pilcher, and Hynes (1970) and a successful surgical correction following clinical diagnosis was reported by Hansing, Young, and Rowe (1972).

There is an analogous condition in which the dividing membrane is situated very low in the atrium and presentation is that of a supravalvar tricuspid stenosis; Folger (1968) reported 2 such cases and Nakano and his colleagues (1974) described a surgically corrected case.

This malformation should not be confused with a supernumerary right-sided venous chamber caused by dilatation of either the coronary sinus or an anomalous pulmonary vein, as these structures are not parts of the right atrium proper.

The case presently described is of further interest in that the right ventricle is divided by a unique malformation of the tricuspid valve.

Case report

No clinical history is available; the specimen is known to be from a female child (J.C.); from the size of the heart she was probably between 3 and 6 months old.

Externally the atria are not remarkable, but internally the right atrium is divided in a sagittal plane so as to produce the appearance of three atrial cavities lying side by side. The right lateral compartment (Fig. 1A) consists of the trabeculated portion of the atrium and the auricular appendix. The only direct venous inflow to this compartment is from the normally situated coronary sinus. The cavity opens directly into the blind inlet portion of the anomalous right ventricle and the only egress is through a small opening just above the orifice of the coronary sinus which communicates with the medial portion of the divided right atrium.

The medial right atrial compartment is approximately 1.5 cm in diameter and extends the full length and depth of the atrial portion of the heart. It receives the superior vena cava and the inferior vena cava, both of which are normally situated and it communicates inferiorly with the right lateral atrial compartment. The left wall of this middle atrial cavity is deficient, permitting communication through a wide 0.8 cm diameter opening with the morphological left atrium. The presence of the limbus fossa ovale enables this connexion to be identified as an ostium secundum defect. The right wall of the middle atrial chamber is a lax membrane which is attached superiorly to the summit of the atrial wall immediately to the right of the superior vena cava opening. Posteriorly it is attached throughout the length of the crista terminalis and inferiorly it approaches the sinus septum and the inferior limbus of the interatrial septum, thus enclosing the inferior vena cava. At this lower margin it presents a crescent-shaped border to the

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[1] R.H.A. is a British Heart Foundation Senior Research Fellow.

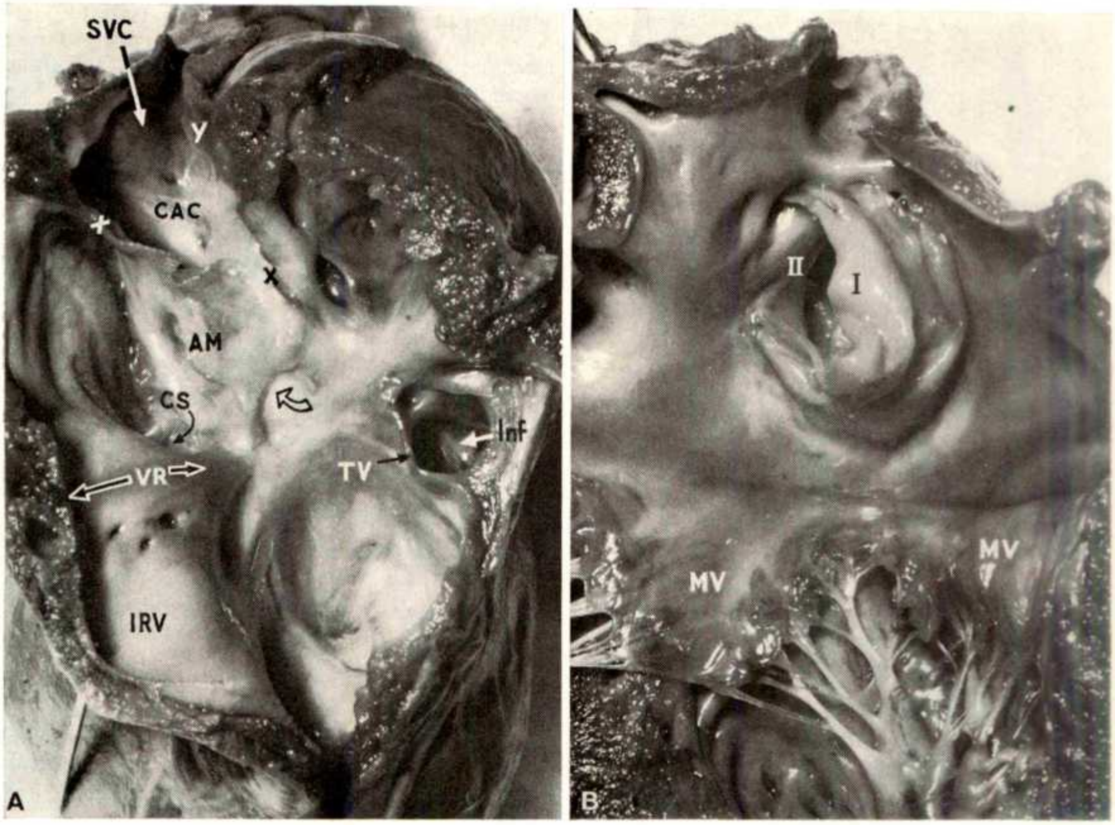

FIG. 1 *A) The right side of the heart opened laterally showing the division of the right atrium by the atrial membrane (AM), which has been incised in the upper portion along the lines xx and xy to reveal the opening of the superior vena cava (SVC) into the central atrial compartment (CAC). The coronary sinus orifice is indicated (CS) and the adjacent opening in the atrial membrane is marked by the open arrow. The bare valve ring (VR) lies between the right atrium and the inlet portion of the right ventricle (IRV) which has a smooth atrialized wall. The vestigial medial portion of the tricuspid valve (TV) separates the inlet portion from the infundibular portion (inf.); these structures have been opened by the plane of incision, there is no natural communication between the infundular cavity and any other cardiac chamber, neither has it any outlet as the pulmonary valve is atretic. B) The medial wall of the left atrium showing the aneurysmal portion of the septum primum (I) through the opening of which can be seen the smooth margin of the septum secundum (II). The mitral valve (MV) is normally formed.*

small 0.25 cm diameter communication with the right lateral cavity (Fig. 1A). Anteriorly the partition is attached to the atrial wall on a line passing downwards from the cleft between the superior vena cava orifice and the opening of the auricular appendix. The posterior wall of this central cavity is smooth and free from muscular trabeculations.

The left atrium is of normal configuration and receives the normal pulmonary veins. The wall between it and the central cavity exhibits the normal features of the left side of the interatrial septum, with an ostium secundum defect. The very lax septum primum portion of the septum bulges aneurysmally into the left atrium (Fig. 1B).

The left atrium opens into the normal left ventricle through a normal mitral valve (Fig. 1B). The right atrioventricular valve is grossly abnormal; the major portion of the valve ring is smooth and shows no trace of the valve. The entrance into the ventricle is wide and unguarded, and the appearances are those of Ebstein's anomaly with atrialization of most of the lateral and anterior walls of the hypoplastic right ventricular inlet chamber (Fig. 1A). On the medial aspect of the valve ring a vestigial valve cusp forms an occluding partition across the right ventricle completely separating the inlet chamber from a diminutive, 1.5 cm long, 0.5 cm diameter, outlet chamber which extends to the site of the atretic pulmonary valve.

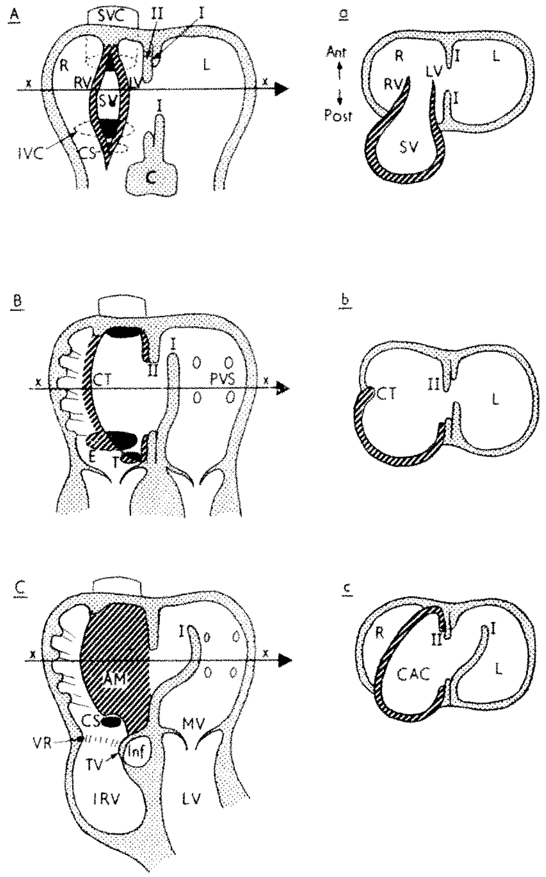

FIG. 2 *Diagrams showing the structures involved in atrial septation: A. embryonic; B. normal mature state; C. Cor triatriatum dexter (present case). The inset diagrams a, b, c, represent cross-sectional views in the planes xx as indicated. R, right atrium; L, left atrium; SV, sinus venosus; RV, right venous valve; LV, left venous valve; C, atrioventricular cushion; CT, crista terminalis; E, Eustachian valve; T, Thebesian valve; PVS, pulmonary veins; IVC, inferior vena cava; other symbols as for Fig. 1.*

The great vessels are in normal relation, the pulmonary artery trunk is atretic, and the ductus arteriosus is patent.

Discussion

As with other reported cases of cor triatriatum dexter, the right atrial partition is undoubtedly derived from an abnormal and persistent right venous valve. In early stages of cardiac development the opening of the sinus venosus into the right atrium is guarded by two prominent folds, the right and left venous valves, which join superiorly to form the septum spurium. As the sinus venosus becomes progressively incorporated into the right atrium, these valves separate and regress. The remnant of the left venous valve merges with the atrial septum secundum. The right venous valve normally disappears except for the Eustachian and Thebesian valves at the lateral margins of the inferior vena cava and coronary sinus, respectively. These orifices are separated by the inferior limbic band or sinus septum. The site of the remainder of the right venous valve is indicated by the crista terminalis, a ridge which separates the pectinate muscle region of the primitive right atrial chamber from the smooth portion which is derived from the sinus venosus.

The position of attachment of the atrial partition in this case, together with the absence of a separately recognizable Eustachian valve, identifies it as being the portion of the right venous valve superior to the sinus septum. Such an anomaly corresponds to type 2 in the classification of Doucette and Knoblich (1963). In most similar cases the antero-inferior margin of the persistent venous valve presented a prominent free edge, often thickened and cordlike; in the present case there is an unusual degree of attachment to the anterior wall, and communication between the two portions of the right atrium is minimal and provides solely for the coronary venous flow across from the right atrium to the left.

Cases of this anomaly dying during infancy and childhood generally have atresia or stenosis of the pulmonary valve, usually in conjunction with atresia or hypoplasia of the right atrioventricular valve. Coexisting Ebstein's anomaly of the tricuspid valve has also been described (Dubin and Hollingshead, 1944). Though the contention that there is a special association between the two anomalies has been rejected by Hudson (1965), the present case lends support to such a hypothesis.

A remarkable feature of this case is that the tricuspid valve is imperforate in addition to exhibiting Ebstein's anomaly. The valve presents a dense membrane at the junction of the hypoplastic inflow and outflow portions of the right ventricle. Such imperforate Ebstein anomalies are very rare; one of us (R.H.A.) has seen one additional example in association with a ventricular septal defect but the present case is associated with an intact ventricular septum. We are unaware of any previous description of this anomaly. Though this condition can correctly be called tricuspid atresia, it is important to distinguish it from the commoner form of tricuspid atresia. The latter anomaly more closely resembles a state of morphologically single ventricle with outlet chamber. Thus, the supposed site of the atretic valve points to the primitive ventricle and not to the 'right' ventricle. In contrast, in the present case the imperforate valve interposes between the inlet and outlet portions of a developed but hypoplastic right ventricle.

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British Heart Journal, 1976, **38**, 112–116.

Granulomatous mitral valve obstruction

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Acquired non-rheumatic valvular mitral valve obstruction is extremely rare. A case of mitral valve obstruction is described which resulted from a granulomatous mass replacing the valve cusps. The problems in diagnosis and probable aetiology are discussed.

Acquired non-rheumatic valvular obstruction involving the mitral leaflets is extremely rare. Obstruction to left ventricular inflow may be caused by tumours and other masses in the left atrium which prolapse through the mitral orifice during ventricular diastole. All these are rare and include left atrial myxomas and malignant neoplasm as well as fungal masses and ball thrombi. We describe a case of non-rheumatic granulomatous mitral valvular obstruction with associated pulmonary lesions and discuss both the diagnostic problems and probable aetiology.

Case report

The patient, a 42-year-old Grenadan woman, was first seen in the chest clinic at Hammersmith Hospital in 1967 because of persistent hoarseness. At that time the chest radiograph was normal and a Heaf tuberculin test negative. However, cultures from two laryngeal swabs grew an atypical scotochromogenic mycobacterium of doubtful significance. Annual chest radiographs were taken and in 1972 first showed the development of bilateral apical opacities. In 1972 the patient had an uneventful eighth and twin pregnancy. She had at no time had rheumatic fever or contact with tuberculosis.

When she was initially examined in March 1974 the only significant cardiovascular abnormality was a soft pansystolic murmur. When admitted to hospital in May 1974 she had developed florid signs of pulmonary hypertension with early right ventricular failure, and showed an increased 'a' wave in the venous pulse in the neck, parasternal heave, and delayed accentuated pulmonary component of the second heart sound. The pansystolic murmur was still present and in addition there was now a dull opening snap but no mid-diastolic murmur. The electrocardiogram had also changed from normal in March to show right ventricular hypertrophy, which later became more distinct (Fig. 1). Serial chest radiographs from 1972 showed the development of pulmonary venous hypertension and left atrial enlargement together with the bilateral apical opacities.

The haemoglobin was 11·4 g/dl; WBC 8000 (63% lymphocytes); ESR (Westergren) 80 mm in one hour. Protein electrophoresis showed a pronounced increase in gammaglobulin and immunoglobulins IgG 3360, IgM 206, IgA 484 mg/100 ml. Tests of thyroid and adrenal function were normal. Mantoux test was negative 1:10 000. Multiple cultures of sputum, urine, gastric aspirate, bone marrow, and laryngeal swabs were negative for myocobacteria. An echocardiogram (Fig. 2) showed a mobile yet stenotic mitral valve. However, in several views multiple echoes may be seen between the abnormally moving posterior echo, which is separated from the anterior cusp even in systole. Cardiac catheterization confirmed that there was pronounced pulmonary arterial and venous hypertension. Pressures were: pulmonary artery 60/30 mmHg (8/4 kPa); pulmonary wedge (mean) 26 mmHg (3·5 kPa); left ventricle 110/9 mmHg (14·6/1·2 kPa) with an indirect mitral valve gradient of 16 mmHg (2·1 kPa) at end diastole. The left ventriculogram showed mild mitral regurgitation with unusual trapping of contrast medium behind the mitral valve cusps. In retrospect, the pulmonary arterial follow-through injection shows a filling defect in the position of the mitral valve (Fig. 3).

Antituberculosis chemotherapy was instituted because of the *x*-ray appearances of apical tuberculosis, and it was decided to replace the mitral valve. However, while waiting for surgery the patient was readmitted in acute pulmonary oedema. On 16 December 1974 a mitral valve replacement was carried out by Mr. Brian Pickering. The left atrium was opened transversely. The mitral valve leaflets could not be recognized. In their place was a smooth, tumour-like mass some 2 cm thick and forming two lumps 3 cm long not bounded by the mitral ring but extending to the aorta and left pulmonary veins. It was covered with apparently normal endothelium, and attached to the underside were normal chordae and papillary muscles. The mass was excised and a 30-mm Starr-Edwards valve inserted. There was some difficulty in attaching the valve ring securely as several stitches had to pass through abnormal tissue.

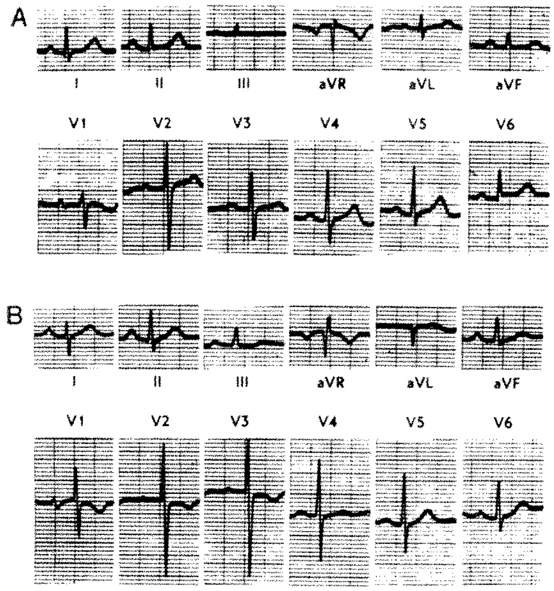

FIG. 1 *Electrocardiograms (A) March 1974, (B) November 1974, showing rapid development of left atrial and right ventricular hypertrophy.*

The tissue removed at cardiotomy consisted of two large fragments, measuring 4×3×1·5 and 3×2·5×1·5 cm, and a number of smaller pieces of papillary muscle, chordae, and fibrous tissue (Fig. 4). The large fragments were firm, with glistening, slightly bosselated superior surfaces, and gradually merged with the chordae at the free margins of the valve cusps. The chordae did not appear thickened or shortened and there was no fibrosis of the papillary muscle tips. The cut surface of the large fragments presented a mottled yellowish grey appearance with a translucent rim on the superior surface. No verrucae were evident on the valve cusps nor was there calcification in the tissue. Microscopy of the valve showed complete replacement of normal architecture by coalescent granulomata containing a central zone of necrosis surrounded by palisaded histiocytes, with scattered giant cells and a mantle of lymphocytes (Fig. 5). In the more fibrous 'endocardial' zone many typical Anitschkow myocytes were evident (Fig. 6) together with histiocytic cells containing SSD- and ZN-positive material. No residual elastica of the valve could be identified. Interestingly, the reticulin framework persisted in the areas of necrosis. Staining of the tissue by various methods failed to show any evidence of mycobacteria, spirochaetes, rickettsia, fungi, or more commonplace organisms.

After surgery the patient initially made a good recovery but a soft systolic murmur became audible before discharge. While at convalescence she became very dyspnoeic and developed severe congestive cardiac failure. A loud pansystolic murmur was noted. Left ventricular angiography showed dehiscence of the mitral valve ring with a paraprosthetic regurgitant jet and gross reflux of contrast medium into the left atrium. On 14 February 1975 the mitral prosthesis was explored and the posterior, inferior border of the mitral valve ring found to be loose. The mitral valve ring was buttressed with Teflon and the prosthesis resutured. She has since made an excellent recovery and currently is being treated with antituberculous chemotherapy. Subsequent Mantoux reactions (1:100), skin tests for atypical mycobacteria (*M. kansasi, M. battey,* and *M. scrofulaceum*), and a Kveim test were negative.

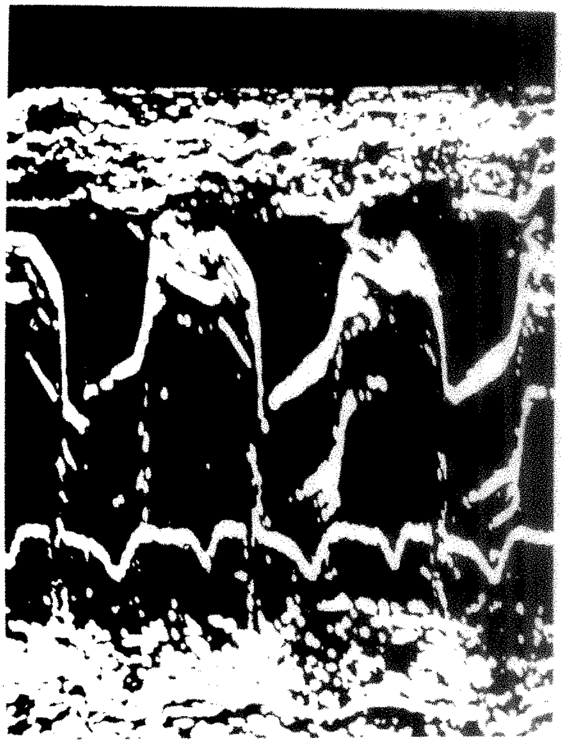

FIG. 2 *Echocardiogram of mitral valve area showing structure with two interfaces separated in both diastole and systole.*

Discussion

The diagnostic problems posed by this case are of particular interest. There were strong reasons for doubting that the patient had simple rheumatic mitral valve stenosis. At the age of 42 she had rapidly developed symptoms and signs of severe pulmonary hypertension over the course of a few months yet had uneventfully survived a twin pregnancy only two years previously. There was also good evidence of systemic disease (WBC, ESR, immunoglobulins). To our surprise, angio-

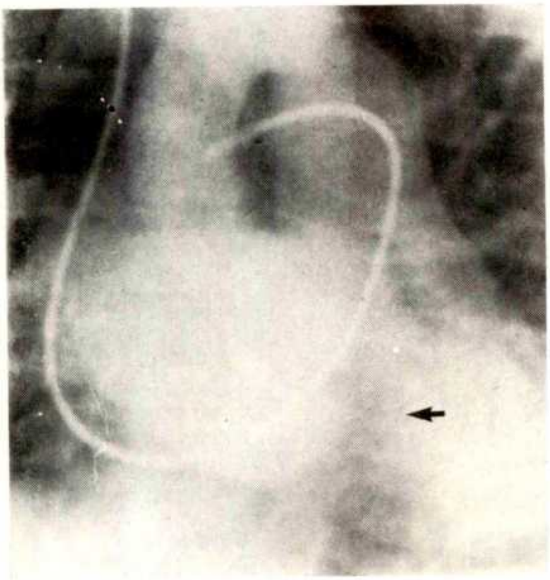

FIG. 3 *Pulmonary arteriogram PA view. L atrial and ventricular phase showing filling defect in position of mitral valve.*

graphy showed no evidence of a left atrial myxoma and the echocardiogram was thought to be compatible with valvular mitral stenosis. Retrospectively, it is apparent that both investigations provided clues to the real nature of the valvular obstruction.

Granulomatous lesions of the endocardium are recorded in both tuberculosis and sarcoidosis. True tuberculous endocarditis is excessively rare (Mark, 1938; Davie, 1936; Baker, 1935), but tuberculomas have been reported to obstruct blood flow in the right atrium (Eisenmenger, 1900) and pulmonary outflow tract (Raws *et al.*, 1968). Sarcoidosis usually affects only the myocardium but endocardial vegetations of the aortic and mitral valves have been reported (Faivre *et al.*, 1956). There have been no reports of endocardial sarcoidosis obstructing blood flow or producing valvular stenosis. Mitral regurgitation consequent on papillary muscle involvement has been described in a patient with myocardial sarcoidosis (Raftery, Oakley, and Goodwin, 1966).

In the present case the associated pulmonary lesions and granulomatous replacement of the mitral valve cusps make either tuberculosis (typical or atypical) or sarcoidosis must likely. The preservation of an endocardial layer excludes an endocarditic process such as described in the patient with sarcoidosis (Faivre *et al.*, 1956), or tuberculous endocarditis (Mark, 1938). Sarcoidosis is favoured by the preservation of the reticulin pattern in the central necrotic zones of the endocardial layer together with the persistently negative tuberculin tests, despite the absence of a positive Kveim reaction. An atypical mycobacterium could possibly cause similar features, and as such an organism was

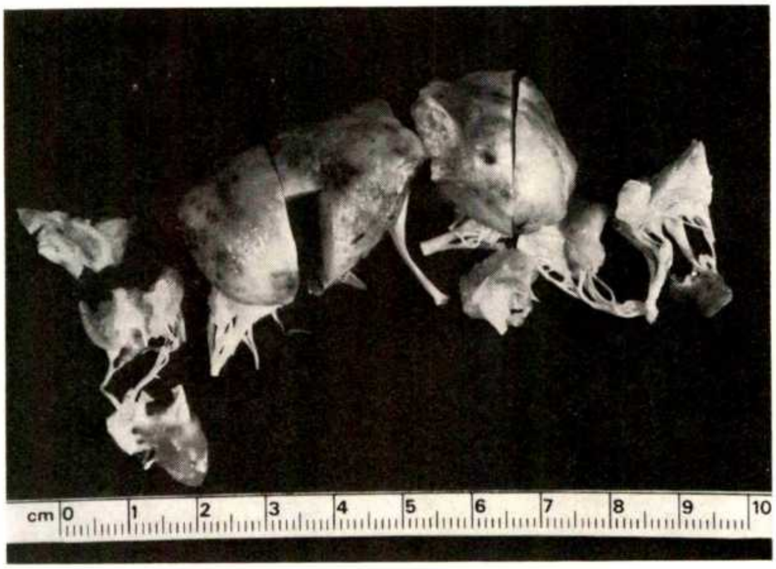

FIG. 4 *Excised mitral valve ring, tumours, chordae, and papillary muscles.*

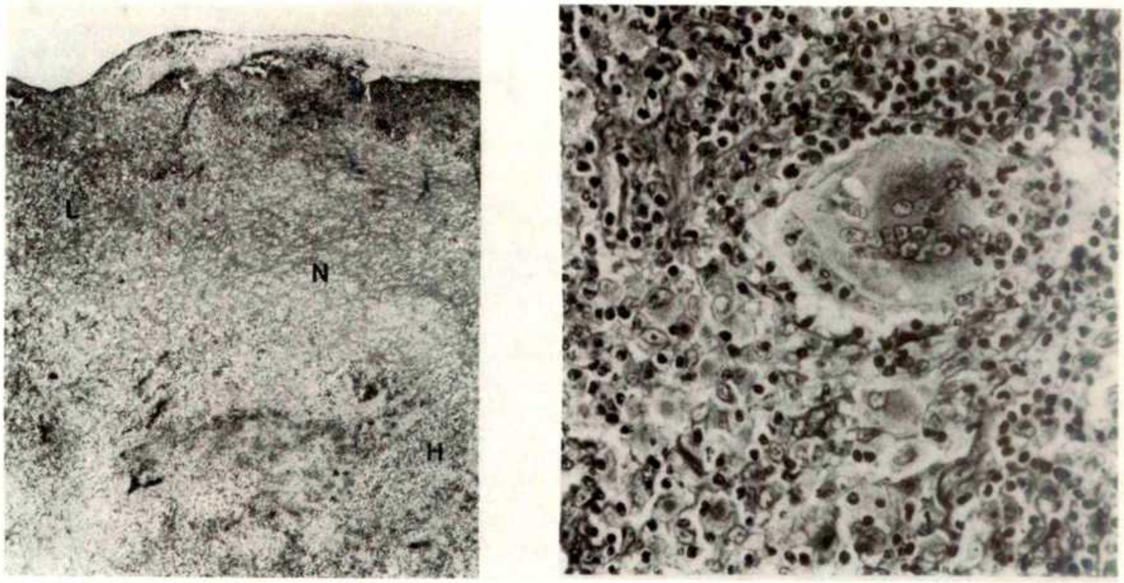

FIG. 5 *Left: Low power view of granuloma. N=central necrosis; H=palisaded histiocytes; L=lymphocytic surround. (H. and E. ×50.) Right: Constituent cells of granuloma. Lymphocytes, histiocytes, and multinucleate giant cells. (H. and E. ×500.)*

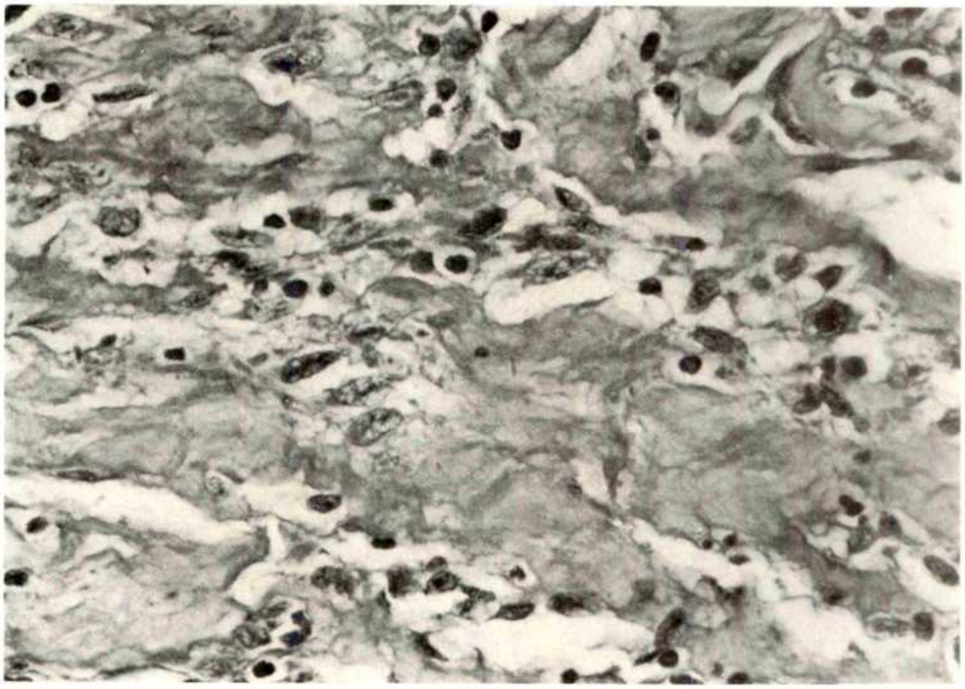

FIG. 6 *Anitschkow 'myocytes' in subendocardial region of valve cusps. (H and E. ×625.)*

isolated in 1967 (though a scotochromogen) this aetiology must remain a distinct possibility.

We thank Dr. E. Sweeney for interpreting the histology.

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Addendum

Since this report was submitted, follow-up chest *x*-rays have shown the development of fine nodular shadowing throughout both lung fields. These changes have occurred while the patient was on full antituberculous chemotherapy and are consistent with a diagnosis of sacoidosis.

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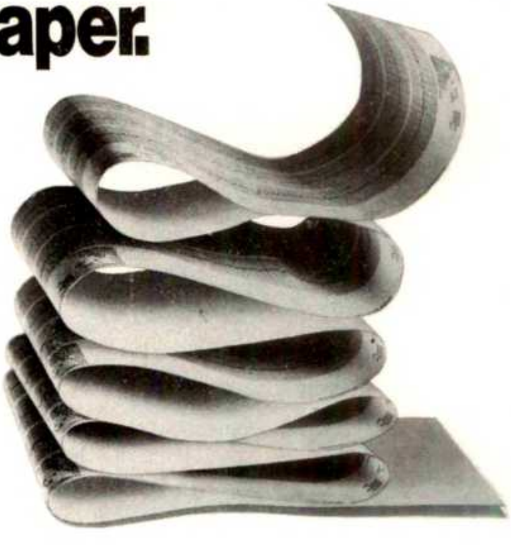

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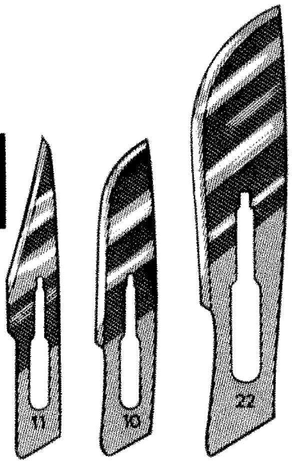

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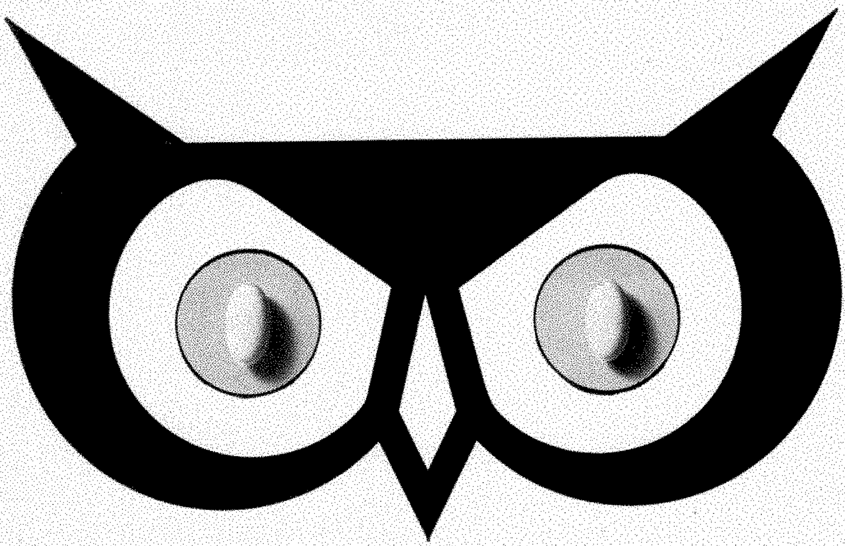

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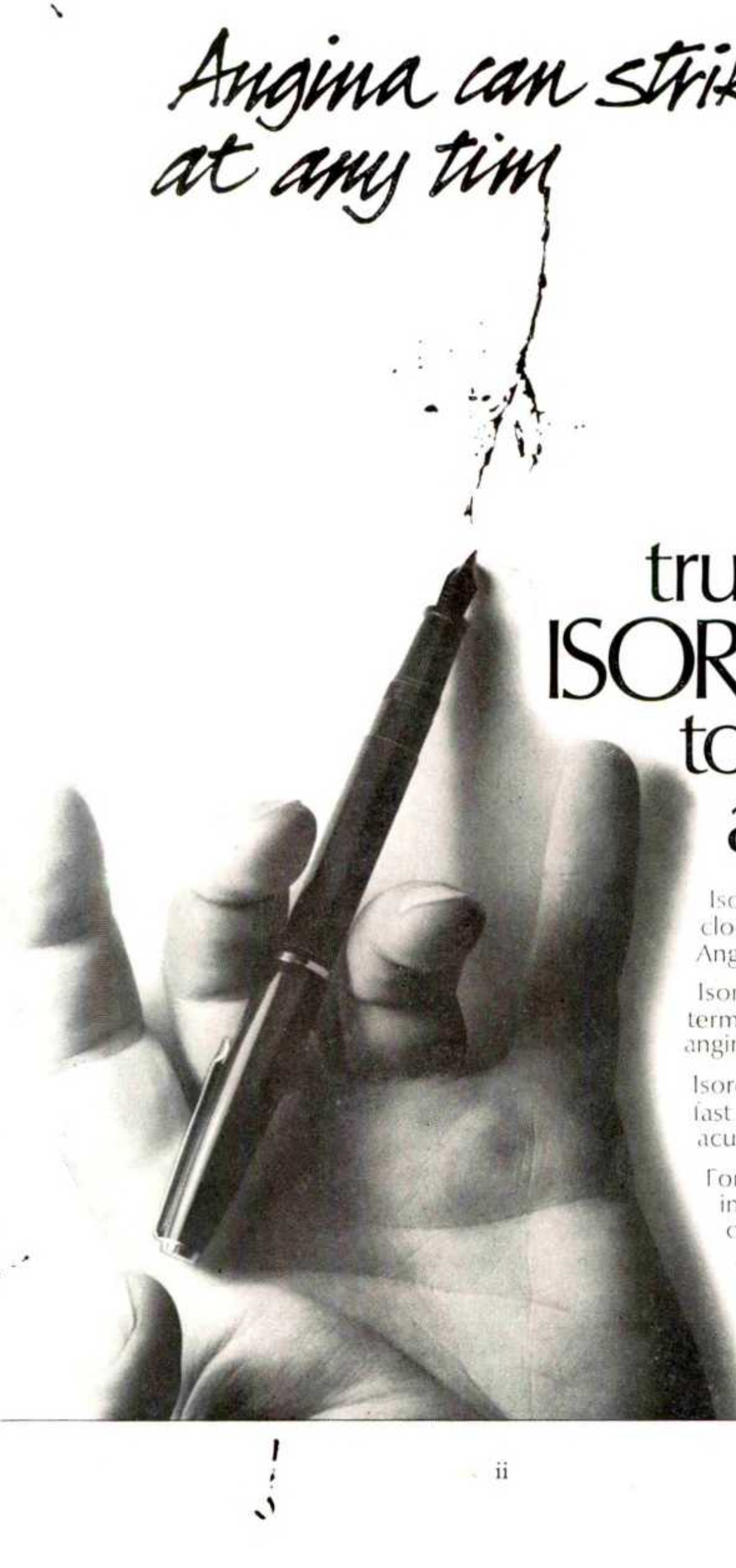

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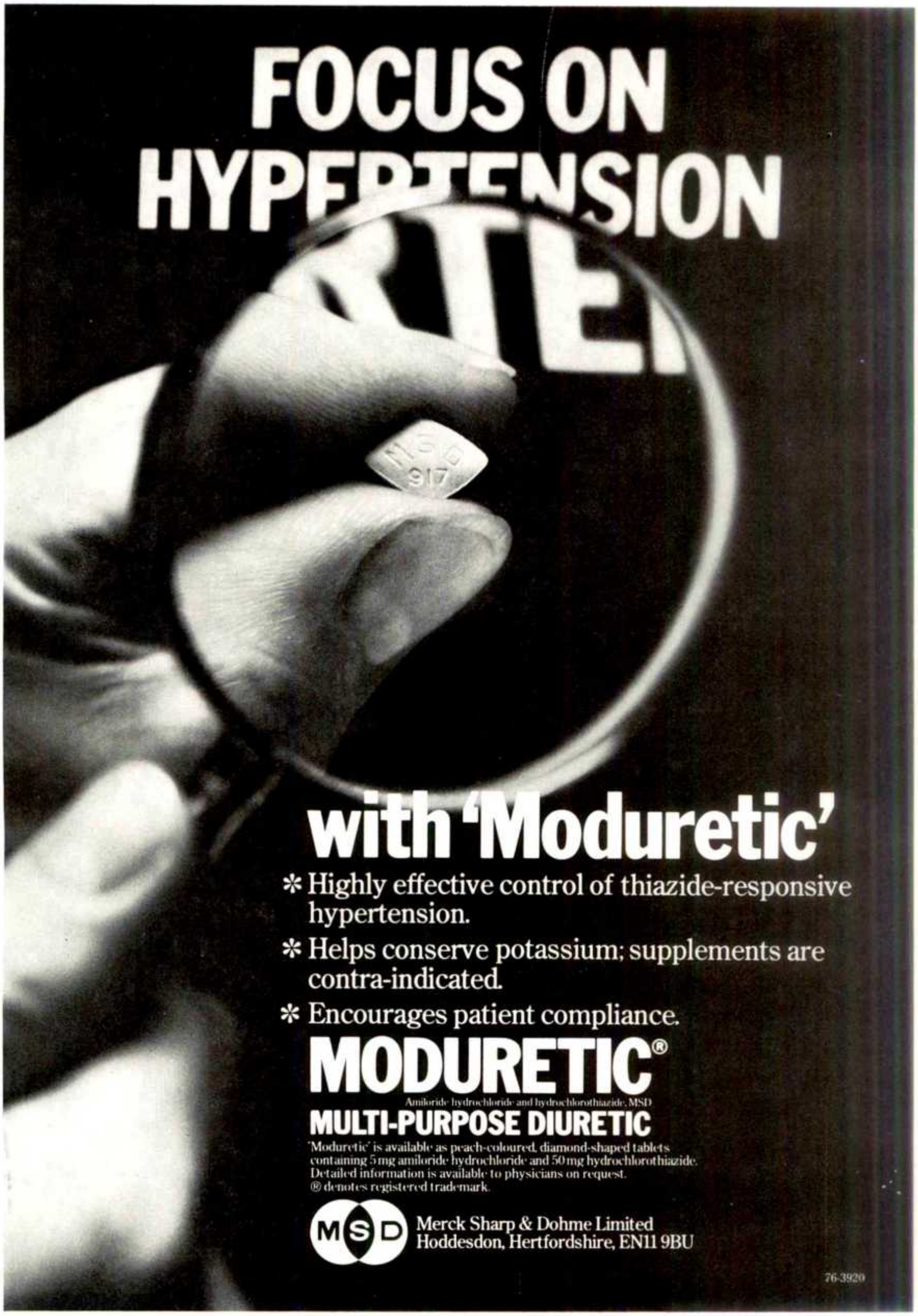

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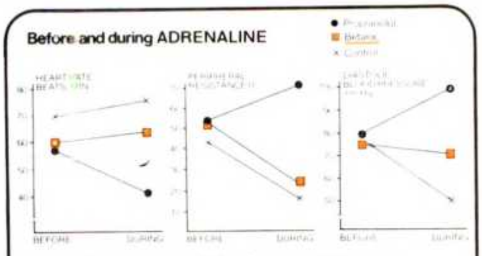

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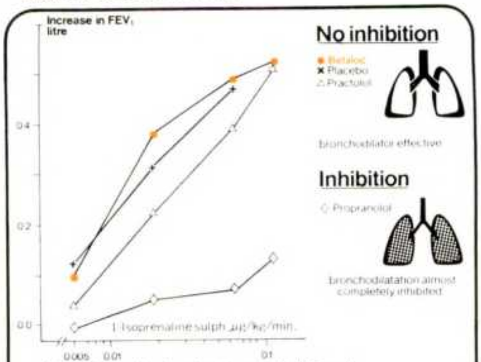

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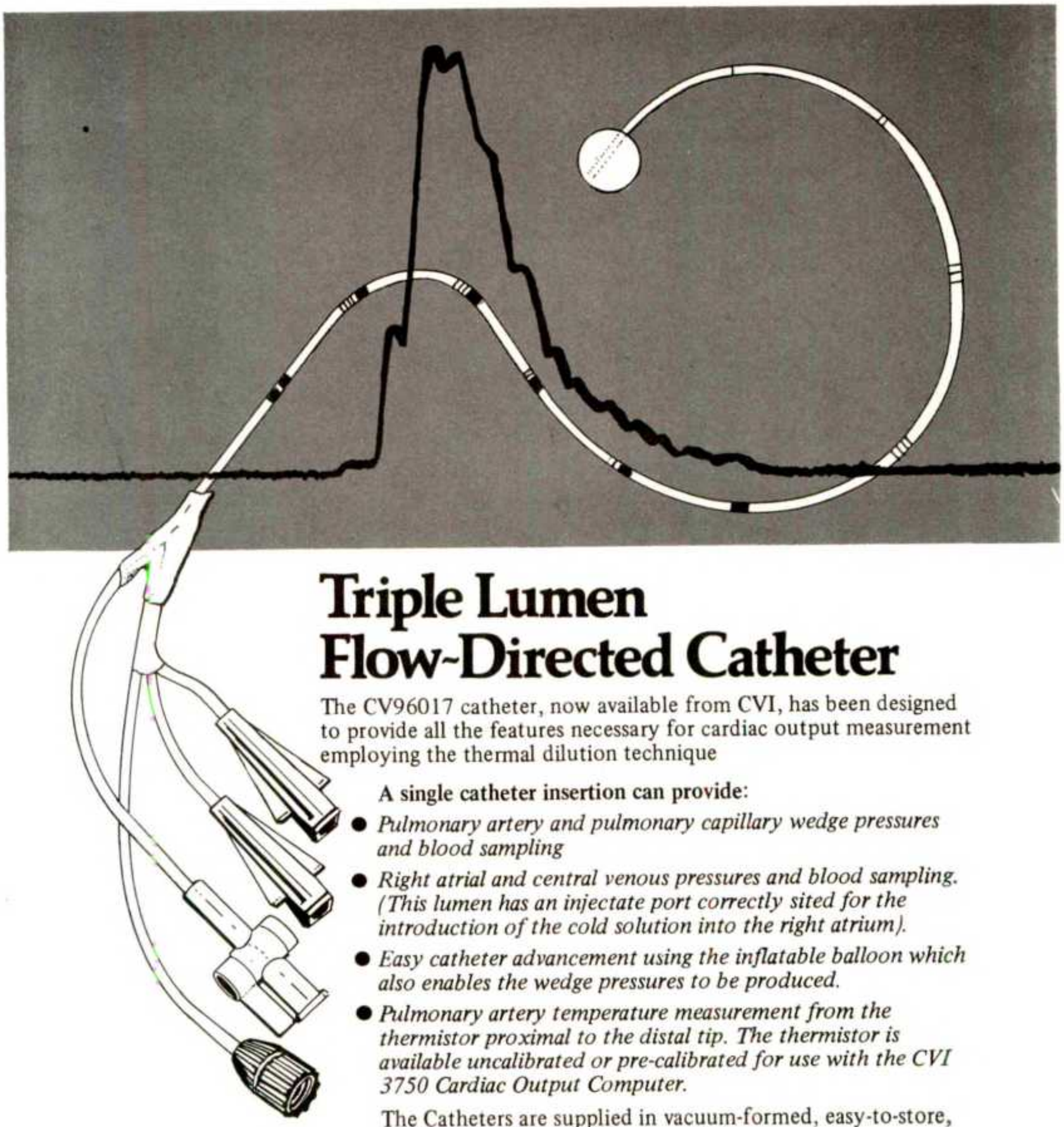

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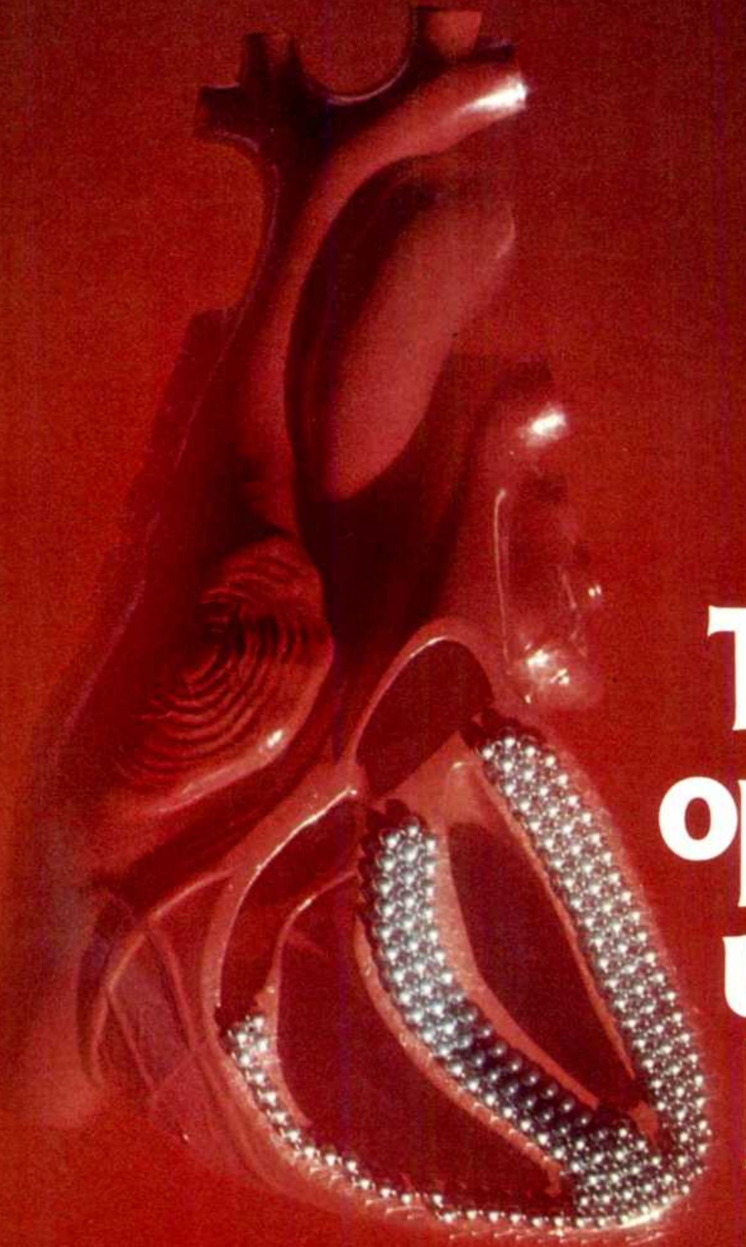

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Editorial

British Heart Journal, 1976, **38**, 117–120.

Torsade de pointes, an atypical ventricular tachycardia

Dennis M. Krikler[1] and Paul V. L. Curry[1]

> 'What's in a name? That which we call a rose
> By any other name would smell as sweet'
> W. Shakespeare, *Romeo and Juliet*, II, ii, 43

When defining a 'new' arrhythmia it is reasonable to suppose that it may indeed have been recognized many years previously. This applies to the disorder now called *torsade de pointes*, whose features have been so well worked out since it was characterized by Dessertenne (1966, 1967). As the opening quotation implies, why introduce a new name? The specific characteristics of this arrhythmia are poorly recognized in English and American reports and the importance of principles relating to its aetiology and management are so crucial that it deserves to be better known; as its mechanism is not yet quite clear a morphological name seems more appropriate. Reference to a standard French-English dictionary (*Harrap's New Shorter French and English Dictionary*, 1967) shows how well *torsade de pointes* describes the appearances: '*torsade*, twisted fringe, ... twist, coil, . . . thick bullion (of epaulet); *pointe*, point (of pin, sword, etc.), tip, head (of arrow, lance) . . .'. Its use in French is much more euphonious than translations like 'wave bursts'.

Though the electrocardiographic features were first noted more than 50 years ago (MacWilliam, 1923; Wiggers, 1929), it is only since Schwartz, Orloff, and Fox (1949) and Schwartz and Hallinger (1954) described 'transient ventricular fibrillation' that its importance has been recognized. Nevertheless, the syndrome still receives inadequate attention: it is not mentioned in a recent otherwise excellent editorial on ventricular tachycardia (Fisch and Noble, 1975), and examples are published under other guises in Anglo-American textbooks on electrocardiography or arrhythmias. If, however, we turn to the French literature for authoritative reviews (Brochier, Motté, and Fauchier, 1972; Slama *et al.*, 1973; Puech, 1974), apparently obscure ventricular tachyarrhythmias that have proved difficult to classify become understandable (Bleifer *et al.*, 1974; Pilling and Nanton, 1974; Meijler, Robles de Medina, and Zimmerman, 1975; Schamroth, 1975).

Diagnostic features

The main features have been summarized and depicted diagrammatically elsewhere (Krikler, 1974). The diagnosis is made from the electrocardiographic appearances both during and between attacks and from any aetiological factors (Slama *et al.*, 1973). The specific findings (best seen when multiple simultaneous leads are taken) consist of paroxysms of ventricular tachycardia in which the QRS axis undulates over runs of 5 to 20 beats, with definite changes in direction (Fig.). This has led to the use of a variety of descriptive terms for what are clearly isolated examples of this disorder, including 'paroxysmal ventricular fibrillation' (Loeb *et al.*, 1968), 'transient recurrent ventricular fibrillation' (Tamura *et al.*, 1967) and 'cardiac ballet' (Smirk and Ng, 1969). But these morphological criteria can be deceptive, since *torsade de pointes* is sometimes associated with fairly long runs of uniform QRS complexes and conventional ventricular tachycardia can be bidirectional (Slama *et al.*, 1973).

Attacks may be brief, consisting of only a few complexes (when diagnosis may be difficult and be

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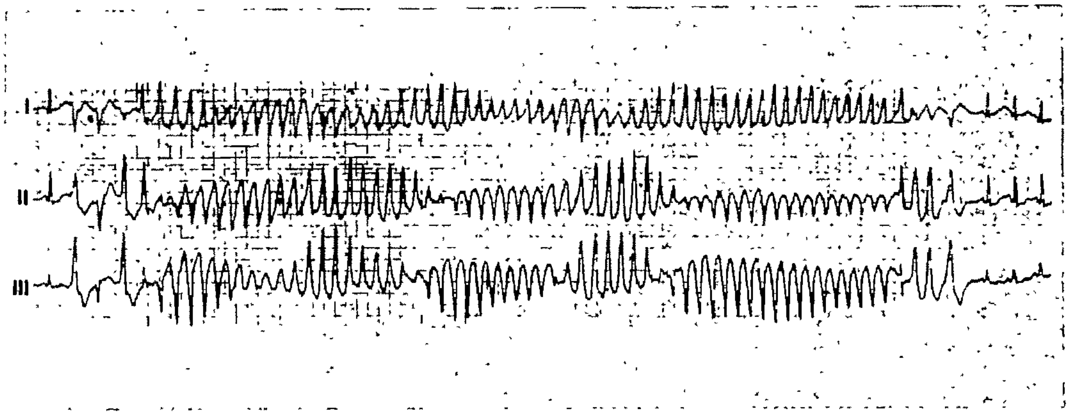

FIG. *Simultaneous recording of leads I, II, and III from a patient with Conn's syndrome showing* torsade de pointes. *Sinus rhythm is shown in the first, and in the last three, beats in which the QT appears prolonged; precise measurement is impossible because the succeeding P waves are merged with the preceding T waves. The first four beats of the arrhythmia show tachycardia, bidirectional in leads II and III, succeeded by a run of tachycardia with wide QRS complexes in which the QRS axis rotates, in an undulating fashion, the differences being well shown by comparison of the three leads. The last run of* torsade de pointes *is prolonged, and the QRS complex is more uniform, with a closer resemblance to classical ventricular tachycardia, the arrhythmia terminating with another change in axis for the last four beats.*

aided by identification of the underlying features), or prolonged, as in the Figure, when syncope may result. When an attack stops spontaneously it is often with a ventricular complex intermediate in form between the QRS of the basic tracing and that seen in tachycardia, though sometimes the final beat is identical to the initiating ventricular extrasystole. Some cases do, however, progress to ventricular fibrillation, and death is an ever-present risk in untreated *torsade de pointes.*

The start of the tachycardia is of both diagnostic and pathogenetic importance. Whereas ventricular tachycardia may follow an early ventricular extrasystole falling on the T wave of the preceding sinus beat (Smirk, 1949), in *torsade de pointes* the initiating extrasystole is usually late, and if, as is often the case, the QT interval is prolonged there is a longer period in which asynchrony of cardiac activity exists (Pick and Katz, 1963). It is tempting to describe the appearances as indicating chaotic cardiac action but, as Dessertenne (1973) points out, the features reflect a well-organized electrical process: clearly there is mechanical inefficiency leading to poor cardiac output, often with syncope. We have noted the initiation of *torsade de pointes* in four patients as a result of intracardiac electric stimulation (Evans *et al.,* 1976), and think that this supports deductions—that can be made from the morphological appearances and the fact that there is usually underlying evidence of impaired repolarization—that the arrhythmia is due to a re-entry mechanism (Raynaud *et al.,* 1969).

Aetiology

A cardinal aspect of *torsade de pointes* is the underlying aetiological situation, which can often be seen or suspected in the basic electrocardiogram of the patient (Table). Of major importance are bradycardias, very often high-grade atrioventricular or sinoatrial block. While the precise mechanism is unclear, it has been suggested that this favours desynchronization of cardiac activation (Han and Moe, 1964; Han *et al.,* 1966; Motté *et al.,* 1970): the occurrence of ventricular tachycardia in a patient suffering from heart block suggests that it is *torsade de pointes.* Hypokalaemia may also provide electrocardiographic clues and should be excluded in all cases of *torsade de pointes*; retrospective analysis of hypokalaemia-induced ventricular arrhythmias may show them to have been caused by *torsade de pointes* (Tamura *et al.,* 1967), and we have recently found *torsade de pointes* caused by Conn's syndrome and familial periodic paralysis (Krikler *et al.,* 1976). While hypomagnesaemia is much less common—and certainly less often looked for—it has been identified as a cause of *torsade de pointes* (Loeb *et al.,* 1968).

Ventricular tachycardia is clearly a major cause of death in patients with the congenital syndromes in

TABLE *Recognized causes of* torsade de pointes

1) Slow basic rhythm
    a) Sinoatrial depression/disease
    b) High-degree AV block
2) Electrolyte deficit(s)
    a) Potassium
    b) Magnesium
3) Congenital QT prolongation syndromes
    a) Overt, with deafness
    b) *Forme fruste*
    c) Concealed
4) Drugs
    a) Cardioactive agents: quinidine, lignocaine, procainamide, prenylamine, etc.
    b) Psychotropic agents: phenothiazines, *tricyclic antidepressants, ? other major tranquillizers
5) Cardiac ischaemia
6) Myocarditis

which the QT interval is prolonged, whether with deafness (Jervell and Lange-Nielsen, 1957) or without (Romano, Gemme, and Pongiglione, 1963; Ward, 1964); indeed it may be present as a *forme fruste,* with QT prolongation only apparent after exercise (Von Bernuth *et al.,* 1973). In at least some of these cases the ventricular arrhythmia appears to be *torsade de pointes* (Motté *et al.,* 1970).

For many years ventricular tachyarrhythmias have been known as a complication of quinidine therapy (Levy, 1922), and as this drug acts in part by prolonging repolarization it is not surprising that *torsade de pointes* should be seen (Acierno and Gubner, 1951; Rainier-Pope *et al.,* 1962), more often as a result of overdosage than idiosyncrasy (Brochier *et al.,* 1972). Though other drugs with an action resembling that of quinidine were not noted as causes of *torsade de pointes* by Brochier *et al.* (1972), we have seen it twice (a new observation, which makes it less than coincidence) after an overdose of lignocaine (unpublished observations). Several cases of the arrhythmia have been caused by prenylamine, possibly because of its quinidine-like effects (Bens *et al.,* 1973). In its own right digitalis has not been incriminated, and we would not expect it to cause *torsade de pointes* as it shortens the repolarization time. If it occurs attention should be focussed on any concomitant medications—for example, potassium-losing diuretics or quinidine. Among non-cardiac drugs that may induce *torsade de pointes* are phenothiazines, notably thioridazine (Schoonmaker, Osteen, and Greenfield, 1966), and tricyclic antidepressants. We have seen *torsade de pointes* followed by ventricular fibrillation after an overdose of amitryptiline (unpublished observations): in sinus rhythm the QT had been prolonged, and this persisted when haloperidol was substituted, the interval returning to normal when all psychotropic agents were stopped.

Torsade de pointes is a known but rare complication of myocardial infarction (Dalle, Meltzer, and Kravitz, 1967), occurring so seldom perhaps because of lack of associated asynchrony of repolarization (Puech, 1974), but it has been recognized during the course of so-called Prinzmetal (variant) angina. When this is associated with paroxysmal atrioventricular block (Chiche, Haiat, and Steff, 1974) the pathogenesis could be that of atrioventricular block of any cause, but its occurrence in this disorder in the absence of heart block (Benaim *et al.,* 1975) implies the presence of subtle factors encouraging re-entry. Histologically-proven myocarditis has been incriminated in a single patient (W. Somerville, 1975, personal communication), and we are aware of another unpublished case.

Treatment

Certain of the aetiological factors provide important clues to the therapy of *torsade de pointes.* It is absolutely vital not to interpret the appearances as representing ventricular hyperexcitability, for quinidine and similar agents given on this assumption may disastrously aggravate the arrhythmia (Brochier *et al.,* 1972). We have on two occasions had to use direct-current countershock when *torsade de pointes* led to ventricular fibrillation (Krikler *et al.,* 1976; Evans *et al.,* 1976), but this has only a temporary effect. Clearly the underlying situation must be corrected—for example, potassium should be replaced and quinidine or other drugs withdrawn—but urgent action is needed upon diagnosis. The first step should be to infuse isoprenaline intravenously to shorten repolarization time and thus avoid a state of asynchronous depolarization; while this is being done cardiac pacing may be instituted. When heart block is the underlying cause of the arrhythmia this is the definitive therapy; when other causes are present it helps while such corrective measures as are feasible—for example, potassium infusion—are undertaken. Right atrial pacing at 100 to 120 beats a minute usually suffices, the increased rate shortening repolarization and providing less opportunity for re-entry (Brochier *et al.,* 1972); if there is AV block the ventricle must of course be paced.

Torsade de pointes can thus be seen to constitute a definable arrhythmia with important aetiological, pathogenetic, diagnostic, and therapeutic features: its recognition is not an academic matter because it requires urgent treatment quite different from that of classical ventricular tachycardia.

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British Heart Journal, 1976, 38, 121–128.

Change in symptoms of hypertensive patients after referral to hospital clinic

C. J. Bulpitt, C. T. Dollery, and S. Carne

From the London School of Hygiene and Tropical Medicine, the Royal Postgraduate Medical School, London, and the Grove Health Centre, London

At their first visit to a hospital clinic 178 patients referred with a diagnosis of hypertension were given a self-administered questionnaire. They received a similar questionnaire 12 months later. Of the 178 patients 99 were not initially on treatment. Similarly 78 normotensive subjects were drawn randomly from the local population and sent a second questionnaire 10 months later. The symptoms at the first visit of the normotensive controls, the untreated hypertensive patients, and 477 patients on long-term treatment in the hypertension clinic were compared. Treated and untreated hypertensive patients complained more of nocturia and also of unsteadiness either on standing or in the morning. Treated hypertensives complained more of sleepiness, dry mouth, diarrhoea, and, in men, impotence and failure of ejaculation. Similarly, untreated hypertensives complained of excessive depression, blurred vision, and waking headache.

Fifty-five of the normotensive subjects and 110 of the newly referred hypertensive patients responded to the second questionnaire. The proportions losing and gaining symptoms were calculated together with the proportions always complaining and never complaining of a symptom. Hypertensive patients tended to lose the complaints of unsteadiness and headache but to gain the symptoms of vivid dreams, a slow walking pace, and diarrhoea. The net improvement for a symptom was defined as the excess of patients who lost a symptom over those who gained the symptom, expressed as a percentage. Over the follow-up period the control subjects had a net improvement averaged over 14 symptoms of +2·4 per cent. A similar result was obtained for the hypertensive patients of +2·0 per cent, the symptoms lost being balanced by those gained.

The changes in symptoms with time were related to the changes in blood pressure and it is suggested that only headache, 'unsteadiness, lightheadedness, or faintness' and nocturia can actually result from raised blood pressure and then only in a proportion of patients complaining of these symptoms.

Treating mild hypertension is expected to reduce morbidity and mortality and also perhaps symptoms. On the other hand, the patients have to take medicine daily which may produce side effects. To provide more information on the symptoms caused by hypotensive therapy we devised a self-administered questionnaire on those symptoms thought to be related to the level of blood pressure and on those of the known side effects of hypotensive drugs (Bulpitt, Dollery, and Carne, 1974). It included questions on waking headache; nocturia; weakness of the limbs; walking pace; sleepiness; hours of sleep; unsteadiness; dry mouth; diarrhoea; frequency of defaecation; depression; and, in men, impotence, failure of ejaculation, and the frequency of sexual intercourse.

Received 11 July 1975.

The present paper compares the symptoms of normal controls and hypertensive patients newly referred to hospital as recorded in the questionnaires at their first visit and after 10 to 12 months. The results are compared with a previous survey of hospital patients on long-term treatment (Bulpitt and Dollery, 1973).

Methods

Three surveys were conducted. Questionnaires were given, firstly, to 582 patients on long-term treatment who attended the Hammersmith Hospital hypertension clinic over a three-month period; secondly, to 212 patients with hypertension newly referred to the corresponding medical outpatients over a one-year period; and, thirdly, to 173 persons randomly selected from a local general practice register. The 582 patients were sent a questionnaire by post and asked to bring it completed at their next hospital visit: 105 (18%) either failed to attend for an appointment or failed to complete the questionnaire. Patients who did not receive the questionnaire were excluded from the study population only if the questionnaire was 'returned to sender'. People in the general practice group were asked to complete the questionnaire and attend the practice surgery for measurement of their blood pressure. Despite one postal reminder only 88 (51%) returned the questionnaire. The 212 'new' patients were given the questionnaire to take away at the time of their first hospital visit. When necessary one reminder was sent: 178 (84%) returned the questionnaire. Details of drug treatment and blood pressure were added to the information derived from the questionnaire. In the new patient and general practice groups the following questions, to be answered 'yes' or 'no', were added: (The other questions have been published elsewhere (Bulpitt *et al.*, 1974).)

Are you often troubled by a blocked or runny nose?

Compared to other men (women) of your age, are your powers of concentration better than average? Same as average? Worse than average?

Within the last three months have you often been troubled by vivid dreams or nightmares?

Within the last three months have you often felt sick or vomited?

Seventy-eight of the 88 general practice subjects were neither hypertensive nor on hypotensive drugs and 99 of the 178 new patients were not on treatment. The questionnaire was sent a second time on average 10 to 12 months later to the general practice subjects and to the hospital new patients. The response rate from the 88 general practice subjects was 75 per cent: one had died, two had moved, and 21 failed to reply. The response rate from the 178 hospital new patients was 66 per cent. Four had died, eight moved, and 56 failed to reply (response rates confined to those who had not moved).

Statistical methods

The Fig. represents the results obtained when giving the same question to N patients on two occasions; 'a' patients do not have the symptom on either occasion, 'd' patients have the symptom on both occasions, 'b' patients gain the symptom on the second questionnaire, and 'c' patients lose the symptom. Intuitive measures of repeatability, for example $(a+d)$ N, vary with the prevalence of the symptom, and therefore repeatability was defined as $1-(bc/ad)$ (R. G. Carpenter, 1975, personal communication). This measure will equal zero when the repeatability is due entirely to chance, and will equal 1 when $b+c=0$. In practical terms, however, repeatability cannot be calculated when either a, b, c, or $d=0$.

		Second answer	
		No symptom	Symptom present
First answer	No symptom	a	b
	Symptom present	c	d

FIG. *Assessment of repeatability*

Results

Relationship between symptoms, disease, and receiving treatment

Table 1 shows a comparison of the complaints recorded on the first questionnaire by the normotensive subjects, the hypertensive patients on long-term treatment, and the untreated hypertensive patients. The results of a $2\times n\ \chi^2$ to detect any significant differences between the three groups are given in the last column. When a significant result was obtained two of the columns were pooled and compared with the remaining column. When the symptom was considered to be a side effect of treatment—for example, dry mouth, diarrhoea, sleepiness, impotence, and failure of ejaculation—the treated group was compared with the untreated and normotensive patients. When a symptom was thought to be associated with hypertension independent of treatment—for example, nocturia or faintness—the hypertensive groups were compared with the normotensive subjects. Waking headache, blurred vision, and depression appeared to be symptoms predominantly of untreated hypertension and were compared with the normotensive plus treated group.

Dry mouth, impotence, and failure of ejaculation appeared to be associated with therapy and occurred mainly in the group receiving treatment ($P<0{\cdot}001$ for each comparison). A similar result was found with sleepiness ($P<0{\cdot}01$) and diarrhoea ($P<0{\cdot}05$). Nocturia and faintness occurred predominantly in the hypertensive groups, with or without treatment ($P<0{\cdot}001$ for both symptoms). The untreated hypertensives suffered more from waking headache ($P<0{\cdot}001$), depression ($P<0{\cdot}01$), and blurred vision ($P<0{\cdot}05$). A slow walking pace occurred most often in the treated group and was intermediate in the untreated hypertensive patients. This was also true for diarrhoea and sleepiness. The relation between individual drugs and these symptoms has already been reported (Bulpitt and Dollery, 1973).

TABLE 1 *Complaints in normotensive subjects, untreated hypertensive new patients, and long-term treated hypertensive patients. Asterisks within table refer to χ^2 comparisons between one result and the results underlined in other columns*

	Normal subjects	*Untreated hypertensives*	*Treated hypertensives*	*Significance of $2 \times n$ χ^2 test*
Total No.	78	99	477	
Average age	53	51	55	
Mean lying blood pressure (mmHg)	136/80	174/100	160/95	
Female (%)	62	57	52	NS
Sleepiness (%)	31·4	43·2	51 4**	**
Hours of sleep	7·4	7·2	7·3	NS
Dry mouth (%)	20 5	23·7	40·2***	***
Unsteadiness on standing or in morning (%)	7·9***	35·4	33·5	***
Nocturia (%)	45·3***	68·4	73·2	***
Diarrhoea (%)	15·5	25·8	30 4*	*
Frequency of defaecation/day	1·2	1·3	1·3	NS
Depression (%)	34·3	44·7**	29·4	**
Blurred vision (%)	14·7	29·8*	20·6	*
Slow walking pace (%)	9 5	24·2	37·0	***
Weak limbs (%)	18·4	34·0	26·4	NS
Waking headache (%)	15·1	31·3***	15·5	***
Nasal stuffiness (%)	26·8	29·7	—	NS
Poor concentration (%)	4 0	12 8	—	NS
Vivid dreams (%)	25·3	27·8	—	NS
Nausea (%)	12 0	19·8	—	NS
Number of males responding	29	41	183	
Impotence (%)	6 9	17·1	24·6***	***
Failure of ejaculation (%)	0	7 3	25·6***	—
Average frequency of sexual intercourse/year	43	50	27	NS

*P < 0·05. **P < 0·01. ***P < 0·001.
NS = not significant.
Conversion: Traditional to SI Units—1 mmHg≈0·133 kPa.

Change in symptoms over 10-month period in normotensive subjects

Table 2 shows the changes in symptoms of 55 normotensive general practice subjects whose initial diastolic blood pressure was less than 100 mm Hg (13·3 kPa) and who did not receive hypotensive drugs (including diuretics and adrenergic beta-blocking drugs). Listed is the proportion of subjects who never had a particular symptom, the proportion of subjects who complained on both occasions, and the proportion of those who gained or lost the symptom. Also given are the repeatability of the questions as defined above and the proportion of subjects who showed a net improvement, where net improvement equals the proportion of patients losing a symptom less the proportion of those gaining the symptom. The net improvement for the symptoms ranged from –6·2 per cent (nasal stuffiness) to 10·0 per cent (sleepiness). The average net improvement was 2·4 per cent. The symptoms most often lost were sleepiness (14·0%) and depression (10·6%). The symptoms most often gained were nasal stuffiness (8·3%) and weakness of the limbs (7·4%). The repeatability of 13 single questions was equal to or greater than 0·95. Three symptoms—morning unsteadiness, faintness, or light-headedness; faintness on standing; and headache on waking in the morning—required more than one question to be answered, and the repeatability was correspondingly lower (0·87 to 0·94).

Table 3 shows the mean change in quantitative variables over a 10-month period in 55 normotensive subjects. Over this period there was little change in the average hours slept, and frequency of defaecation, nocturia, or sexual intercourse.

TABLE 2 *Percentage change in symptoms in 55 normotensive subjects over 10-month period*

Symptoms	*Symptom never present* (%)	*Symptom always present* (%)	*Symptom lost* (%)	*Symptom gained* (%)	*Net improvement* (%)	*Repeatability*
Unsteadiness or faintness	85·2	3·7	9·2	1·8	7·4	0·95
Sleepiness	66·0	16·0	14·0	4·0	10·0	0·95
Weakness in limbs	75·9	11·1	5·7	7·4	−1·7	0·95
Headaches	60·8	27·5	5·9	5·9	0	0·98
Blurred vision	86·8	7·6	3·8	1·9	1·9	0·99
Depression	61·7	21·3	10·6	6·4	4·2	0·95
Diarrhoea	80·0	10·0	6·0	4·0	2·0	0·97
Dry mouth	80·0	10·0	8·0	2·0	6·0	0·98
Nasal stuffiness	66·7	22·9	2·1	8·3	−6·2	0·99
Nocturia	47·2	47·2	1·9	3·8	−1·9	1·00
Slow walking pace	90·2	5·9	3·9	0	3·9	—
Poor concentration	92·2	3·9	1·9	1·9	0	0·99
Nausea	84·9	7·6	3·8	3·8	0	0·98
Vivid dreams	77·8	11·1	9·3	1·9	7·4	0·98
Average	—	—	—	—	2·4	0·97
Multiple questions:						
Morning faintness	98·18	0	0	1·81	−1·81	—
Faintness on standing	90·90	1·82	5·45	1·82	3·63	0·94
Waking headaches	83·63	3·63	7·27	5·45	1·82	0·87
Males*:						
Impotence	94·1	0	0	5·9	−5·9	—
Failure of ejaculation	100	0	0	0	0	—

*Based on replies from 17 men.

TABLE 3 *Mean change in quantitative information over 10-month period for 55 normotensive subjects and over 12-month period for 110 hypertensive new patients (figures in parentheses are numbers contributing to mean)*

	Normotensive subjects	*SEM*	*Hypertensive new patients*	*SEM*
Hours of sleep	−0·14 (50)	0·09	0·07 (103)	0·11
Frequency of defaecation/day	−0·04 (52)	0·04	−0·05 (109)	0·05
Frequency of nocturia (times/night)	0·03 (53)	0·05	0·12 (109)	0·08
Frequency of sexual intercourse (men, times/year)	2·5 (17)	4·7	−2·4 (49)	3·9

SEM=standard error of mean.

Change in symptoms over 12-month period in new hypertensive patients

Table 4 shows the change in symptoms of 110 new hypertensive patients referred with a diagnosis of hypertension. The net improvements for unsteadiness (21·5%), headache (13·6%), unsteadiness on standing (16%), and waking headache (16%) were above the range of results in the control subjects (−6 to +10%), and the net improvements for nocturia (−9·2%) and vivid dreams (−9·6%) were less than expected. Similarly, repeatability was below the expected range for all single questions apart from nocturia and slow walking pace. The symptom of vivid dreams was gained by 17·3 per cent, sleepiness by 15·4 per cent, and weakness of the limbs by 14·3 per cent of the patients. On the other hand, unsteadiness was lost in 25·2 per cent, headache in 19·4 per cent, and nasal stuffiness in 16·0 per cent of patients. The average net improvement (2·0%) for these 14 symptoms was similar to the average for the normal controls (+2·4%).

Table 3 shows the average changes in quantitative variables in the 110 new hypertensive patients. The mean results do not differ significantly from the averages for the normotensive subjects.

Change in treatment over one-year period in new hypertensive patients

Table 5 gives the initial and final therapy in 110 new hypertensive patients. Twenty-four patients (22%) had no treatment and in 32 (29%) the treatment was not greatly altered over the year. When treatment was changed the number starting any one particular treatment was never greater than 12.

TABLE 4 *Percentage change in symptoms in 110 new hypertensive patients over a 12-month period*

Symptoms	*Symptom never present* (%)	*Symptom always present* (%)	*Symptom lost* (%)	*Symptom gained* (%)	*Net improvement* (%)	*Repeatability*
Unsteadiness or faintness	36·4	34·6	25·2	3·7	21·5	0·93
Sleepiness	35·6	35·6	13·5	15·4	−1·9	0·84
Weakness in limbs	45·7	24·8	15·2	14·3	1·0	0·83
Headache	29·1	45·6	19·4	5·8	13·6	0·92
Blurred vision	62·1	18·5	11·7	7·8	3·9	0·92
Depression	43·1	33·3	13·7	9·8	3·9	0·91
Diarrhoea	66·3	13·3	8·2	12·2	−4·1	0·89
Dry mouth	56·9	24·5	7·8	10·8	−2·9	0·94
Nasal stuffiness	54·0	20·0	16·0	10·0	6·0	0·85
Nocturia	24·1	61·1	5·6	9·3	−3·7	0·97
Slow walking pace	58·9	26·2	4·7	10·3	−5·6	0·97
Poor concentration	77·6	9·4	6·5	6·5	0·0	0·94
Nausea	71·2	9·6	12·5	6·7	5·8	0·88
Vivid dreams	62·5	12·5	7·7	17·3	−9·6	0.83
Average	—	—	—	—	2·0	0·90
Multiple questions:						
Morning faintness	65·45	10·0	17·27	7·27	10·0	0·80
Faintness on standing	55·45	13·63	23.63	7·27	16·36	0·77
Waking headache	65·5	10·9	20·0	3·6	16·4	0·90
Males*:						
Failure of ejaculation	90·0	2·0	4·0	4·0	0	0·91
Impotence	80·9	10·6	4·3	4·3	0	0·98

*Based on replies from 52 men.

Change in blood pressure according to change in symptoms

Sixty-four of the 110 new hypertensive patients had a lying blood pressure recorded at the beginning and at the end of the 12-month follow-up period. The fall in lying diastolic (FLD) and systolic (FLS) pressure between the first and last visit was computed together with the average of the two systolic readings (AS) and the two diastolic measurements (AD). The mean (±SEM) AD was 99±2 mmHg (13·2±0·3 kPa). Similarly the mean AS was 171±4 mmHg (22·7±0·5 kPa); mean FLD 16±2 mmHg (2·1±0·3 kPa); and the mean FLS 40±4 mmHg (5·3±0·5 kPa).

Table 6 shows the mean FLD, FLS, AD, and AS according to whether a particular symptom was never present, always present, lost, or gained.

If a symptom is relieved by lowering the blood pressure the patients losing the symptom should show a high mean FLS and mean FLD. The 11 patients losing the complaint of headache had a high mean fall in systolic pressure of 60 mmHg

TABLE 5 *Changes in therapy in 110 new hypertensive patients after one year*

Initial treatment	*Final treatment* None	*Diuretic alone*	*Methyldopa ±diuretic*	*Bethanidine ±diuretic*	*Propranolol ±diuretic*	*Other combination*
None	24	12	9	1	5	5
Diuretic alone	0	7	5	0	1	1
Methyldopa ±diuretic	2	3	18	0	0	6
Bethanidine ±diuretic	0	0	1	1	0	2
Propranolol ±diuretic	0	0	0	0	1	0
Other combination	0	1	0	0	0	5

TABLE 6 *Mean lying systolic pressure (LSP), lying diastolic pressure (LDP), fall in LSP, and fall in LDP, in mmHg, for 64 patients referred with hypertension over 12-month period. Means calculated only for 5 or more patients*

Symptom	*Symptom never present*					*Symptom always present*					*Symptom lost*	
	Average LSP	*Average LDP*	*Fall LSP*	*Fall LDP*	*No.*	*Average LSP*	*Average LDP*	*Fall LSP*	*Fall LDP*	*No.*	*Average LSP*	*Average LDP*
Unsteadiness	165	99	41	21	21	169	98	39	14	23	174	100
Headache	167	98	35	17	18	165	98	32	10	28	176	104
Blurred vision	167	99	38	18	40	172	100	38	7	10	177	102
Depression	170	99	27	20	27	167	96	41	11	18	167	103
Dry mouth	164	97	41	17	37	179	105	45	19	12	174	105
Nocturia	159	97	26	15	14	173	100	42	16	37	—	—
Sleepiness	163	97	37	16	27	176	103	40	12	19	171	98
Weak limbs	166	99	38	18	30	175	101	35	10	17	164	95
Nausea	169	100	45	20	44	—	—	—	—	4	166	97
Vivid dreams	170	101	41	18	40	159	93	41	17	7	—	—
Poor concentration	170	99	38	15	46	171	96	33	9	8	—	—
Nasal stuffiness	171	99	47	18	35	174	101	44	16	8	163	99
Slow walking pace	166	100	36	17	33	179	100	43	8	18	—	—
Diarrhoea	168	100	40	16	43	167	91	17	2	9	—	—
Unsteadiness on on standing	170	100	45	20	31	167	97	24	9	12	170	98
Unsteadiness in morning	170	100	43	19	40	166	99	25	7	7	167	95
Waking headache	170	99	37	18	33	166	95	29	10	8	172	104

Conversion factor from Traditional Units to SI Units: 1 mmHg ≈ 0·133 kPa.

(8·0 kPa) which was compared with the mean drop for other patients, 34 mmHg (4·5 kPa). The difference between the means was significant at the 5 per cent level. A similar high systolic drop (55 mmHg [7·3 kPa]) was noted with 14 patients losing a waking headache. The fall in diastolic pressure did not reach statistical significance. The average fall in systolic pressure of 54 mmHg (7·2 kPa) in 8 patients losing blurring of vision did not achieve statistical significance.

When a symptom is a side effect of a potent hypotensive agent the gain of a symptom may be accompanied by an increased average FLD and FLS. The gain of sleepiness was accompanied by an increased mean FLD (28 mmHg (3·7 kPa) against 14 mmHg (1·9 kPa); $P < 0{\cdot}05$). Similarly, a high average FLS and FLD was observed with patients developing poor power of mental concentration (FLS 63 mmHg [8·4 kPa] and FLD 24 mmHg [3·2 kPa]).

Discussion

The differences between the untreated hypertensive patients and the controls may be due to one of at least four mechanisms: (1) a raised blood pressure; (2) the hypertensive patient's concept of symptoms he should expect; (3) the referring doctor's concept of hypertension-related symptoms which led him to the diagnosis; (4) psychoneurosis associated with hypertension. For example, a man with a headache reports the symptom to his doctor and the doctor suspects hypertension. The blood pressure is taken, found to be raised, the patient is informed that the headache is due to hypertension, and he is referred to hospital. The symptom may be due to the raised pressure or to other causes, but the prevalence of headache in hypertension-clinic patients is high since the blood pressure is often not taken and hypertension not diagnosed in patients without this symptom.

We must therefore examine headache, blurred vision, depression, unsteadiness, and nocturia to see if there is any evidence that they result from a high blood pressure, all five symptoms being in excess in the untreated hypertensive group. Headache and unsteadiness were relieved during the follow-up period, and the patients losing their headache had a significantly higher average fall in systolic pressure over this period. These symptoms may therefore be causally associated with high levels of blood pressure, whereas blurring of vision, depression, and nocturia were not relieved over the 12-month period, the net improvements in hypertensive patients being similar to those in control subjects. In treated patients the frequency of nocturia can be related to both blood pressure

Symptom lost			*Symptom gained*				
Fall LSP	*Fall LDP*	*No.*	*Average LSP*	*Average LDP*	*Fall LSP*	*Fall LDP*	*No.*
41	11	15	—	—	—	—	3
60	22	11	—	—	—	—	1
54	16	8	—	—	—	—	3
35	13	8	172	100	32	13	8
22	10	6	169	94	34	6	5
—	—	4	162	99	51	11	7
47	11	8	179	103	49	28	7
47	17	8	172	100	56	19	7
28	4	8	—	—	—	—	4
—	—	4	169	100	43	16	10
—	—	3	158	113	63	24	5
23	8	10	165	102	35	22	5
—	—	3	161	98	49	24	8
—	—	2	—	—	—	—	4
41	13	17	—	—	—	—	4
36	7	12	165	99	45	20	5
55	17	14	—	—	—	—	3

and treatment (Bulpitt *et al.*, 1974; Bulpitt and Dollery, 1974).

We suggest that raised blood pressure does indeed cause headache, and 'unsteadiness'. Headache and 'unsteadiness' are common in neurotic patients (Riseman and Weiss, 1930; Ayman and Pratt, 1931), and increase in hypertensive patients with the degree of psychoneurosis (Bulpitt, Hoffbrand, and Dollery, 1975). However, for psychoneurosis totally to explain the excessive complaints of headache, we should have to assume that neurosis is improved more when the systolic blood pressure is reduced by an average of 60 mmHg (8·0 kPa) than when it is reduced by 34 mmHg (4·5 kPa). Similarly if psychoneurosis is improved by treatment, why are the net improvements for headache (13·6%) and 'unsteadiness' (21·5%) so much better than the net improvement for 'depression' (3·9%)?

Table 1 indicates, however, that in hypertensive patients at least a half of waking headaches and a quarter of 'unsteadiness on stadding or in the morning' will be unrelated to the height of the untreated blood pressure.

The symptoms which increased during the follow-up of hypertensive patients were probably side effects of drug therapy. The net improvements in sleepiness (–1·9 against +10·0% for controls), dry mouth (–2·9 against +6·0%), diarrhoea (–4·1 against +2·0%), vivid dreams (–9·6 against +7·4%), and slow walking pace (–5·6 against +3·9%) were all worse in the hypertensive patients than in the control subjects. The failure to confirm, in the longitudinal studies, an association between treatment and impotence and failure of ejaculation in men was owing to the patients not being given adrenergic neurone-blocking drugs. Examination of blood pressure changes supported sleepiness as a side effect of treatment. Larger numbers are required to examine separate therapeutic groups and a larger survey has been started of all new patients attending two hypertension clinics over a period of two years.

The repeatability of the questions was satisfactory in the normotensive group and the index 1 – (bc/ad) acts as a standard, independent of prevalence, against which new questions can be judged. The lack of dependence on prevalence is an advantage of this index over other suggested measures of repeatability (Young, 1971; Zeiner-Henriksen, 1972). The index is slightly easier to compute than the measurement proposed by Rogot and Goldberg (1966), though their index can be computed if one cell is zero but not if a marginal total is zero. The average net improvement for all symptoms and both sexes expresses the change in symptomatic welfare of the patients. It is of interest that the normotensive controls showed a positive average net improvement of 2·4 per cent. In the hypertensive patients the relief of certain symptoms was balanced by a gain of side effects to give an average net improvement of 2·0 per cent.

The longitudinal approach with assessment of net improvement may help to establish a health status index (Fanshel and Bush, 1970), which may be used for establishing the benefits or otherwise of the drug treatment of hypertension. Information is being collected on the changes in mortality and morbidity to be expected from treatment (Veterans Administration Cooperative Study Group, 1970; Amery and de Schaepdrijver, 1973; Peart, 1973), and these data should be supplemented by validated, reproducible measures of the symptomatic well-being of patients.

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Echocardiographic evaluation of propranolol therapy for mitral valve prolapse[1]

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This study evaluates the effect of propranolol on the echocardiogram of 8 patients with late systolic mitral valve prolapse. Echocardiograms were performed with the patients on no medication and again while on oral propranolol therapy. Propranolol caused a statistically significant increase in left ventricular volume; however, neither the echocardiographic pattern nor the timing of mitral valve prolapse was altered by propranolol. These findings suggest that factors in addition to left ventricular volume play a role in regulating valvular dysfunction in this condition.

Changes in left ventricular volume appear to be important in changing the timing and extent of mitral valve prolapse (Fontana *et al.*, 1970). Passive tilting, which decreases the left ventricular volume, causes greater prolapse, as determined by angiography (Fontana *et al.*, 1975). Amyl nitrite inhalation, which also decreases left ventricular volume, causes earlier systolic prolapse of the mitral valve compared to control observations, and may even transform the echocardiographic mitral prolapse pattern from late systolic to holosystolic (Winkle, Goodman, and Popp, 1975; Dillon *et al.*, 1971). Propranolol, which increases resting left ventricular end-diastolic volume (Helfant, Herman, and Gorlin, 1971), has been reported to diminish or abolish some of the auscultatory findings in patients with mitral prolapse, suggesting that an increase in left ventricular volume may improve the valvular dysfunction (Zeilenga and Criley, 1973). The present study evaluates the effect of propranolol on the timing and pattern of echocardiographic mitral valve prolapse, in an attempt to determine whether or not propranolol alters the basic valvular abnormality in this condition.

Patients and methods

Eight patients, 7 women and one man, seen at the Stanford University Medical Center, were studied after informed consent had been obtained. All 8 patients had late systolic mitral valve prolapse on echocardiogram. No patient had evidence of heart disease other than the mitral valve abnormality, and all were in sinus rhythm. Seven of the 8 patients had clicks or murmurs (Table), and all 8 had symptoms or arrhythmias characteristic of the mitral valve prolapse syndrome.

Echocardiograms were performed while the patients were taking no cardiac medication and repeated during oral propranolol therapy, which was given in an effort to control symptoms or arrhythmias. The echocardiograms were obtained with an Ekoline 20A Smith-Kline ultrasonoscope, using a 2·25 mHz 0 5 cm diameter transducer, with beam collimation to 5 cm depth. Patients were supine and turned approximately 30° into the left lateral decubitus position, and the mitral valve was recorded with the transducer positioned perpendicular to the chest wall in the third or fourth intercostal space at the left sternal border. Left ventricular volumes were obtained by tilting the transducer slightly inferiorly and laterally to record the maximum left ventricular dimension, at a level just below the free edge of the mitral valve. Simultaneous phonocardiograms were recorded at the cardiac apex in some patients, using a Maico contact microphone filtered to display frequencies of 120 to 500 Hz. A permanent strip-chart recording of this information was made at a paper speed of 50 or 75 mm/s, using an Electronics for Medicine DR8 recorder.

Measurements

From these recordings, various points were identified and dimensions and time intervals measured. The onset of abrupt posterior movement of the posterior mitral valve leaflet during systole was termed the 'P' (prolapse) point (Fig. 1), as described previously (Winkle *et al.*, 1975). The 'C' point of apparent mitral valve closure and 'D' point of apparent mitral leaflet separation at opening were identified as described by Edler *et al.* (1961). In those patients in whom a clear D point could not be

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[1] This work was supported in part by NIH grants.

TABLE *Summary of effect of propranolol on echocardiogram of patients with late systolic mitral valve prolapse*

Case No.		*Heart rate (b/min)*	*Duration of systole (C-D) (ms)*	*Duration of prolapse (P-D) (ms)*	*Prolapse fraction (P-D/C-D)*	*LVEDD (cm)*	*LVEDV (ml)*	*LVESD (cm)*
1	Control	60	380	210	0·55	4·8	111	3·0
	Propranolol 320 mg/day	50	420	250	0·60	5·0	125	3·0
2	Control	62	410	250	0·61	4·8	111	2·8
	Propranolol 80 mg/day	58	430	250	0·58	5·5	166	3·4
3	Control	68	400	270	0·67	5·8	195	3·6
	Propranolol 160 mg/day	56	420	270	0·64	6·1	227	3·7
4	Control	69	370	250	0·68	4·4	85	2·7
	Propranolol 160 mg/day	63	370	250	0·68	4·6	97	2·7
5	Control	80	360	190	0·53	5·6	176	3·4
	Propranolol 160 mg/day	56	400	190	0·49	5·8	195	4·1
6	Control	80	340	210	0·62	4·6	97	2·8
	Propranolol 80 mg/day	54	440	310	0·70	4·9	118	2·9
7	Control	79	370	220	0·59	6·0	216	4·3
	Propranolol 120 mg/day	73	380	230	0·61	6·4	261	4·6
8	Control	68	360	180	0·50	5·0	125	3·1
	Propranolol 160 mg/day	51	370	200	0·54	5·0	125	3·1
Mean	Control	70·8±8·0	373±23	222±32	0·59±0·06	5·12±0·60	140±49	3·21±0·54
	Propranolol	56·9±7·7	404±28	244±38	0·60±0·07	5·41±0·64	164±59	3·44±0·66
	P	<0·005	<0·05	NS	NS	<0·01	<0·01	<0·07

LVEDD and LVEDV, left ventricular end-diastolic dimension and volume; LVESD and LVESV, left ventricular end-systolic dimension and volume; MSC, mid-systolic click; LSM, late systolic murmur; NS, not statistically significant.

determined because of the prolapse, D was defined as the intersection of a line extended through points C and P, with the anterior motion of the mitral valve leaflet at end-systole. From these reference points (Fig. 1), the following time intervals were measured: the duration of systole (C-D), the pre-prolapse interval (C-P), and the duration of prolapse (P-D). The fraction of systole occupied by prolapse (prolapse fraction) was expressed as the ratio $\frac{\text{P-D}}{\text{C-D}}$.

Left ventricular end-diastolic dimension and left ventricular end-systolic dimension were defined as the maximal and minimal separation of the left interventricular septal and left ventricular posterior endocardial echoes. The left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were determined by cubing these dimensions (Popp and Harrison, 1970). Stroke volume (SV) and ejection fraction (EF) were derived using the following equations:

$$\text{SV} = \text{LVEDV} - \text{LVESV}$$

$$\text{EF} = \frac{\text{SV}}{\text{LVEDV}}$$

All measurements were averaged over 5 beats to minimize respiratory variation.

Statistical analysis was performed using the two-tailed t test for matched pairs, comparing control and propranolol data.

Results

The Table summarizes the results of this study. Propranolol, in doses ranging from 80 mg to 320 mg per day, decreased the resting heart rate in all patients (Fig. 2). The decrease in mean heart rate from 70·8±8·0 to 56·9±7·7 beats per minute ($P < 0·005$) (Fig. 2) suggests propranolol produced a physiological degree of beta-adrenergic blockade in these patients.

Ventricular volume

Propranolol increased the left ventricular end-diastolic dimension from a mean value (±SD) of 5·12±0·60 to 5·41±0·64 cm ($P < 0·01$), with an associated increase in mean left ventricular end-diastolic volume from 140±49 to 164±59 ml ($P < 0·01$) (Fig. 3). Propranolol also increased the left ventricular end-systolic dimension and volume, but these changes were of only borderline statistical significance ($P < 0·07$). Propranolol increased the stroke volume from 103±32 to 120±35 ml/beat ($P < 0·03$); however, it did not change the calculated ejection fraction (Table).

LVESV (ml)	*SV (ml)*	*Ejection fraction*	*Phonocardiographic findings*
27	84	0·76	MSC
27	98	0·78	MSC
22	89	0·80	MSC—LSM
39	127	0·77	Not done
47	148	0·76	LSM
51	176	0·78	Not done
20	65	0·76	LSM
20	77	0·79	LSM
39	137	0·78	MSC
69	126	0·65	Not done
22	75	0·77	MSC
24	94	0·80	MSC
80	136	0·63	Normal
97	164	0·63	Normal
30	95	0·76	MSC—?LSM
30	95	0·76	MSC
35·9 ± 20·1	103 ± 32	0·75 ± 0·05	
44·6 ± 26·6	120 ± 35	0·75 ± 0·07	
< 0·07	< 0·03	NS	

Echocardiographic pattern and timing of mitral valve prolapse

While taking propranolol, all 8 patients retained the late systolic pattern of mitral valve prolapse on the echocardiogram. Propranolol did not decrease the apparent redundancy of the mitral valve characterized by multiple echoes seen during systole, nor did it appear to lessen the degree of prolapse toward the left atrium (Fig. 1, 4, and 5).

Propranolol did not influence the timing of echocardiographic mitral valve prolapse. With propranolol there was a slower heart rate, accompanied by an increase in the duration of systole (C-D) ($P < 0\cdot05$), reflecting slight increases in both the pre-prolapse interval (C-P) and the duration of prolapse (P-D). However, neither of the latter changes alone achieved statistical significance. Propranolol did not change the prolapse fraction (P-D)/(C-D) (Fig. 6) and thus did not alter the relative timing of echocardiographic mitral valve prolapse.

Discussion

Left ventricular volume changes seem important in determining the onset and extent of mitral valve prolapse. Decreased left ventricular volume is associated with an earlier onset (Winkle *et al.*, 1975) and a greater amount (Fontana *et al.*, 1975) of mitral valve prolapse. Presumably, increased left ventricular volume produces opposite effects; however, this has never been carefully documented. Recent studies suggest that factors other than left ventricular volume may influence the dynamics of valve prolapse. Clicks, and presumably mitral valve prolapse, occur earlier in the first systole after termination of rapid atrial pacing (Towne *et al.*, 1973). Since left ventricular volume increases with the long pause after termination of pacing, one would expect the clicks to occur later, rather than earlier, in systole. In this context, an effect of increased contractility and/or decreased afterload on valve prolapse dynamics were postulated to account for the earlier occurrence of clicks. It is not known whether contractility or afterload changes alone can alter the timing of mitral valve prolapse. Phenylephrine increases afterload, but usually does not change the timing of clicks (Barlow *et al.*, 1968), though they may occur later in systole (LeWinter *et al.*, 1974).

Complete understanding of the factors influencing mitral valve prolapse is desirable for optimal clinical management of these patients. For example, most patients with mitral regurgitation respond to afterload reduction with a decrease in left ventricular volume and a reduction in the amount of mitral valve regurgitation (Goodman *et al.*, 1974). Patients with mitral regurgitation associated with mitral valve prolapse could, theoretically, show a paradoxical response with an increase in the mitral prolapse and a worsening of the regurgitation. A single patient reported by Bittar and Sosa (1968) did show an increase in angiographically demonstrated mitral regurgitation during amyl nitrite inhalation. This case demonstrates that such a paradoxical response can occur. If increased contractility can cause earlier prolapse, the administration of inotropic agents could potentially worsen valvular dysfunction. The clinical significance of such paradoxical responses and their frequency is unknown at the present time.

In this study propranolol did not alter the timing or echocardiographic pattern of mitral valve prolapse, despite the fact that it caused a slight increase in left ventricular end-diastolic volume. This lack of effect may be partially related to the relatively small increase in left ventricular dimensions after propranolol. In a previous study (Winkle *et al.*, 1975), we demonstrated that amyl nitrite, which causes earlier prolapse and occasionally converts late systolic prolapse to holosystolic prolapse, decreased the left ventricular end-diastolic di-

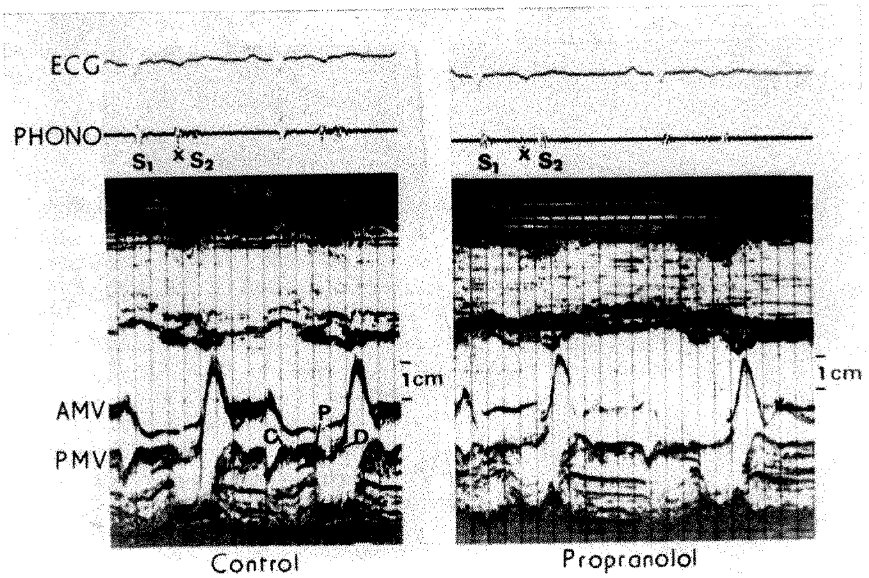

FIG. 1 *Representative control and propranolol echocardiogram (Case 8). The C, P, and D points are labelled in the control echocardiogram. Except for the slower heart rate, the echocardiograms are similar. Behind the dominant, labelled echo, faint echoes characteristic of mitral valve prolapse can be seen in the left atrium, both before and after propranolol.*

mension by an average of 5·5 mm. Propranolol caused an average increase in this dimension of only 2·9 mm, approximately half the change produced by amyl nitrite. This smaller change, relative to the presumed fixed length of the chordae tendineae, may be insufficient to produce a detectable change in the timing or pattern of mitral valve prolapse. However, propranolol also produces changes in heart rate, systemic vascular resistance, arterial pressure, left ventricular filling pressure, cardiac output, and myocardial contractility. The lack of effect of propranolol in these patients, despite a modest increase in left ventricular volume, suggests that some of these factors may influence valve dynamics in patients with mitral valve prolapse.

Although this is an echocardiographic and not a haemodynamic study, it suggests that propranolol does not cause dramatic changes in the valvular dysfunction of mitral valve prolapse. We have performed left ventricular angiograms before and after intravenous propranolol administration in a single patient with late systolic prolapse and could detect no effect on the mitral valve prolapse. Shappell *et al.* (1973) also reported a single patient in whom propranolol did not affect the degree of mitral valve prolapse on angiography. Therefore, on the basis of current knowledge, we conclude that the ability of propranolol to relieve symptoms or abolish serious arrhythmias in some patients with mitral valve prolapse is probably not related to anatomical improvement of the valve dysfunction.

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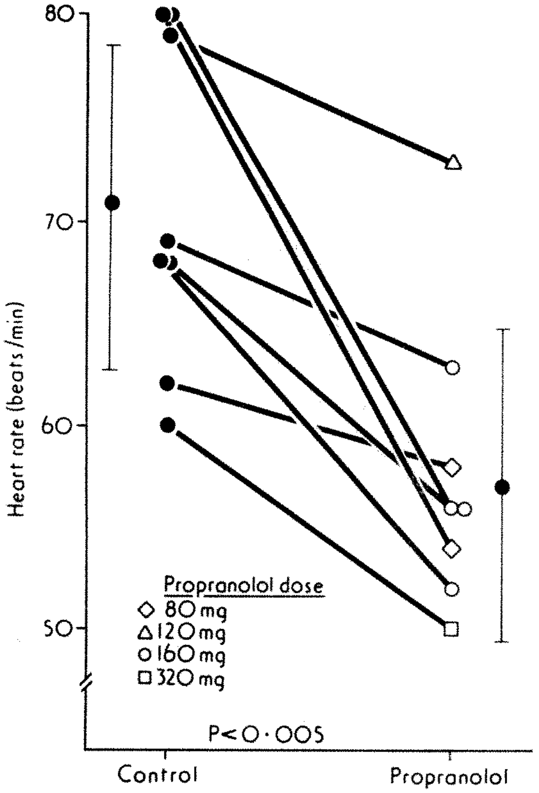

FIG. 2 *The reduction in resting heart rate after propranolol administration is demonstrated for the patients in this study. This reduction was significant at the 0·005 level.*

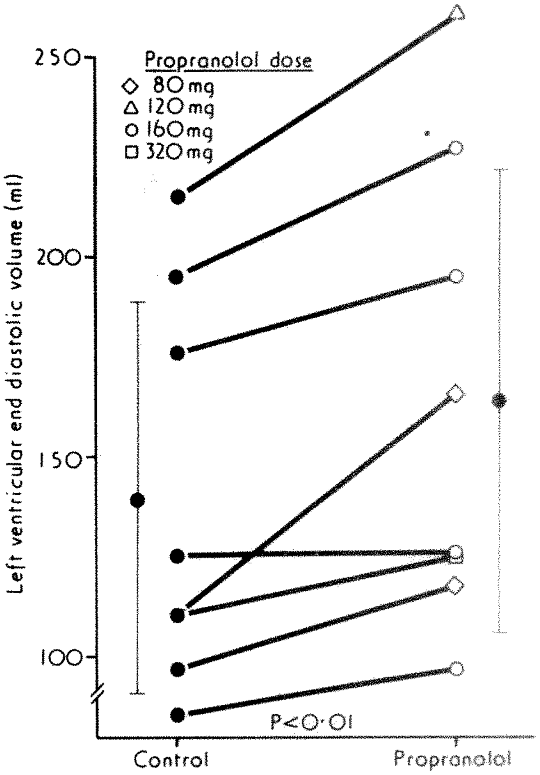

FIG. 3 *The increase in left ventricular end-diastolic volume while the patient was taking propranolol is illustrated. This increase in volume probably reflects compensatory changes to maintain cardiac output at the slower heart rate.*

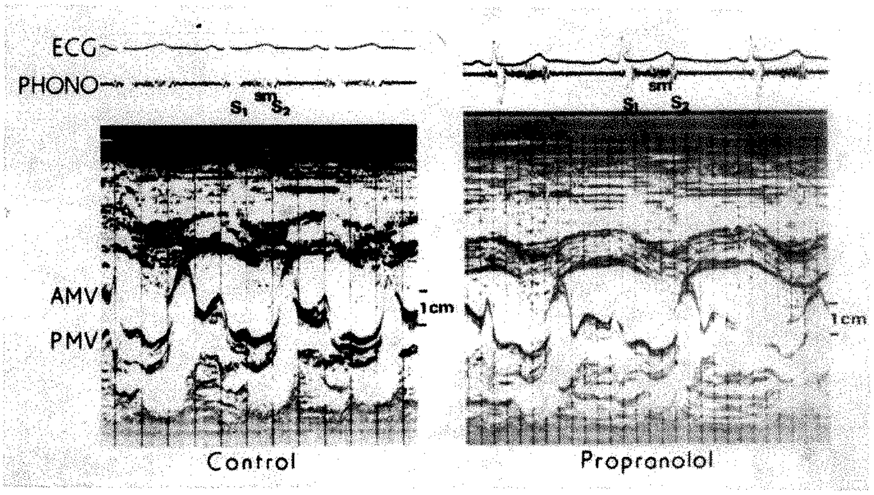

FIG. 4 *Control and propranolol echocardiograms from Case 4. There is no apparent change in the echocardiographic pattern and timing of mitral valve prolapse. A late systolic murmur is seen on both phonocardiograms.*

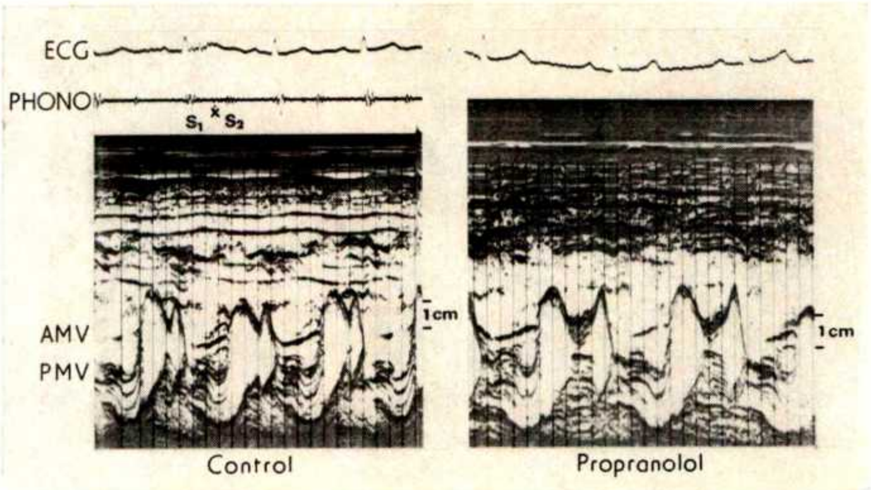

FIG. 5 *Control and propranolol echocardiograms from Case 5. As in Fig. 1 and 4, propranolol does not appear to have altered echocardiographic mitral prolapse or the striking redundancy, appearing as multiple mitral valve echoes during systole, that this patient demonstrates.*

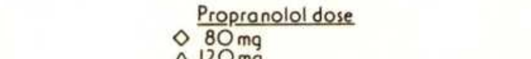

FIG. 6 *The lack of effect of propranolol on the timing of echocardiographic mitral valve prolapse is demonstrated in this figure. The prolapse fraction, the fraction of echocardiographic systole during which the mitral valve is prolapsed, was unaltered by oral propranolol therapy.*

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British Heart Journal, 1976, 38, 135-146.

Opening snap and isovolumic relaxation period in relation to mitral valve flow in patients with mitral stenosis

Significance of A2-OS interval

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In 15 patients with pure or predominant mitral stenosis and in a control group of 11 patients without mitral stenosis the blood flow velocity through the mitral valve orifice was recorded by means of a directional Doppler ultrasound velocity catheter introduced transeptally and positioned in the orifice of the mitral valve. A simultaneous surface phonocardiogram was obtained. The timing of the mitral opening snap in relation to the blood velocity record of the flow through the valve supported the hypothesis that the opening snap is due to a sudden tensing of the valve leaflets by the chordae tendineae. Determination of the exact time of mitral valve opening, made possible by the blood velocity record, led to the division of the classical A2-OS interval (aortic valve closure to opening snap) into two components representing respectively the diastolic isovolumic relaxation period and the time of excursion of the mitral valve cusps. The durations of the isovolumic relaxation period were compared with those in the control patients and were found to correlate with the severity of the mitral stenosis, whereas those of the excursion time of the mitral cusps were influenced by the presence or absence of mitral valve calcification.

Though the importance of the mitral opening snap has been universally recognized, it is piquant to note that 150 years after it was first described (Bertin, 1824) controversy persists over its diagnostic value, mode of production, and time relationship to the isovolumic relaxation period of the left ventricle. It had been considered pathognomonic of mitral stenosis until the possibility was raised of its occurrence in other conditions such as mitral regurgitation (Nixon, Wooler, and Radigan, 1960; Perloff and Harvey, 1962), ventricular septal defect, or persistent ductus arteriosus (Luisada, 1953, 1965; Millward, McLaurin, and Craige, 1973)—that is, in conditions which have in common an excess flow through the mitral valve.

Its genesis has been continually questioned. Many mechanisms have been suggested—among others, two-phase filling of the left ventricle (Bouillaud, 1835) and asynchrony of aortic and pulmonary valve closure (Duroziez, 1862)—until Potain, in Rouchès's thesis (Rouchès, 1888), coined the term *claquement d'ouverture* (opening snap), thereby implying a sudden stretching of the valve leaflet restrained in its excursion by the shrunken, stiff, chordae tendineae. This hypothesis was later supported by the well documented mechanographic correlation studies of Wolferth and Margolies (Margolies and Wolferth, 1932) and eventually was generally accepted. Additional evidence for such a mechanism was provided by cineangiographic studies of the mitral valve (Ross, Criley, and Morgan, 1961; Ross and Criley, 1964; McCall and Price, 1967), which showed that the snap occurred at the time of maximum excursion of the valve leaflet but failed to demonstrate any filling of the left ventricle before the complete opening of the valve. More recently, echocardiographic recording of movements of the anterior leaflet of the mitral valve confirmed a synchrony between the snap and the completion of the rapid movement of the valve (Friedman, 1970; Millward *et al.*, 1973). Rodbard and Libanoff (1972), on the other hand, proposed a new and entirely different mechanism, contending

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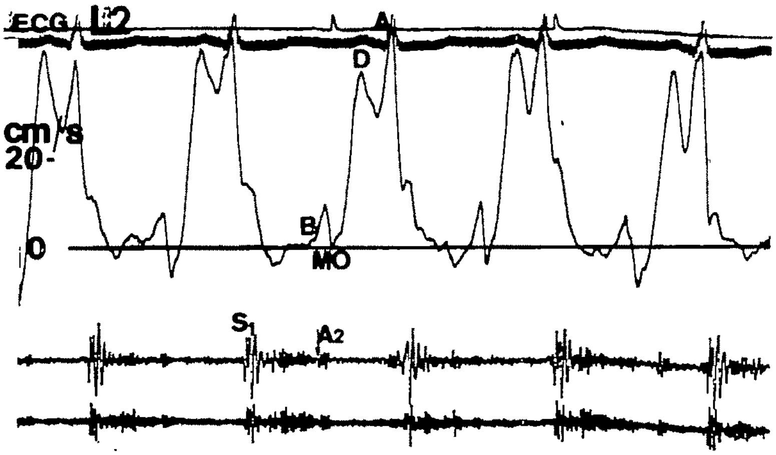

FIG. 1 *Normal mitral valve flow velocity curve calibrated in cm/s. Velocities above zero line refer to flow passing from left atrium into left ventricle, those below zero line refer to flow directed from left ventricle toward left atrium. Note inflexion point B lining up with first vibrations of A2, and inflexion point MO at onset of ascending limb of D wave (true mitral opening). During diastole note two successive waves. D=initial filling wave, A=atrial contraction wave. The usual precipitous negative deflection (ic) lining up with the first heart sound is missing.*

that sudden closure of the valve after the initial opening was in fact responsible for the anomalous sound, which therefore should be called a 'closing snap'. In addition to these irreconcilable explanations, it was still not clear whether blood did or did not flow through the valve at the time of the snap.

Moreover, an apparent close timing relationship between the occurrence of the opening snap (OS), of the O trough of the early diastolic wave of the apex cardiogram and of the crossing point of atrial and ventricular pressure curves led to the now currently accepted assumption that the time interval between the aortic component of the second heart sound and the opening snap (A2–OS) or the O point of the apex cardiogram (A2–O) represented fairly well for clinical purposes the isovolumic relaxation period of the left ventricle (Taquini, Massell, and Walsh, 1940; Rappaport and Sprague, 1942; Fishleder, 1966; Legler, Benchimol, and Dimond, 1963; Coulshed and Epstein, 1963; Deuchar, 1964; Tafur, Cohen, and Levine, 1964; Benchimol and Ellis, 1967; Spodick and Kumar, 1968; Delage *et al.,* 1971). Such an identification, however, was seriously questioned by Di Bartolo (Di Bartolo, Nuñez-Dey, and Bendezú-Prieto, 1962), Tavel (Tavel *et al.,* 1965), Forman (Forman *et al.,* 1967), and, more recently, Willems (Willems, De Geest, and Kesteloot, 1971).

We showed (Kalmanson *et al.,* 1975a) the feasibility of instantaneously recording the mitral valve blood flow velocity (Fig. 1) using transepta Doppler ultrasound catheterization, and we proposed a physiological interpretation of the recorded wave form (Fig. 2). In particular, it was possible to define and measure the isovolumic relaxation period and determine the actual opening point of the mitral valve. We also studied the blood flow velocity patterns through the mitral valve in patients with mitral valve disease (Kalmanson *et al.,* 1975b). These findings led us to study the correlation of the timing of the second heart sound and that of the opening snap in relation to instantaneous mitral valve blood flow phenomena.

Patients

A total of 15 patients (9 women and 6 men) ranging in age from 26 to 60 years was studied. Twelve had pure mitral stenosis and three predominant mitral stenosis associated with mitral regurgitation; six were in sinus rhythm and nine in atrial fibrillation. Routine phonocardiograms were recorded in all patients, firstly, with simultaneous carotid pulse and apex cardiogram recordings and, secondly, with routine diagnostic cardiac catheterization using the transeptal route. A Telco (St. Cloud, France) manometer for pressure measurements and a Waters (Waters, Rochester, Minnesota, U.S.A.) dye dilution apparatus to determine cardiac output were used. The patients were carefully examined for calcification of the mitral valve at fluoroscopy and subsequently at operation (6 cases) or necropsy (1 case). Nine patients had obvious calcification, six had little or none.

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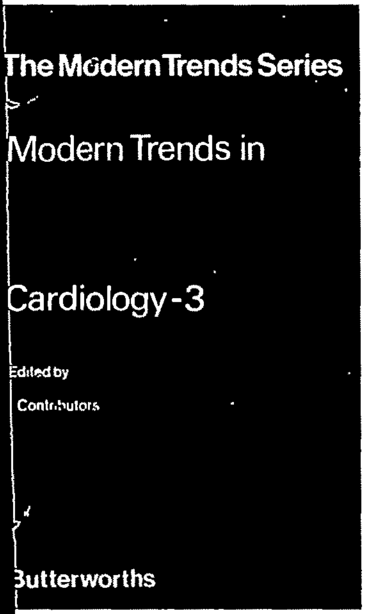
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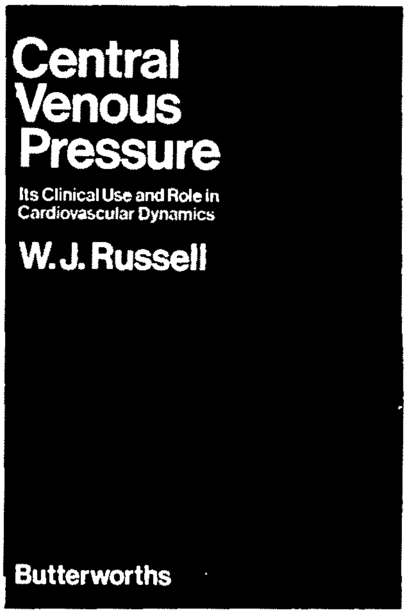

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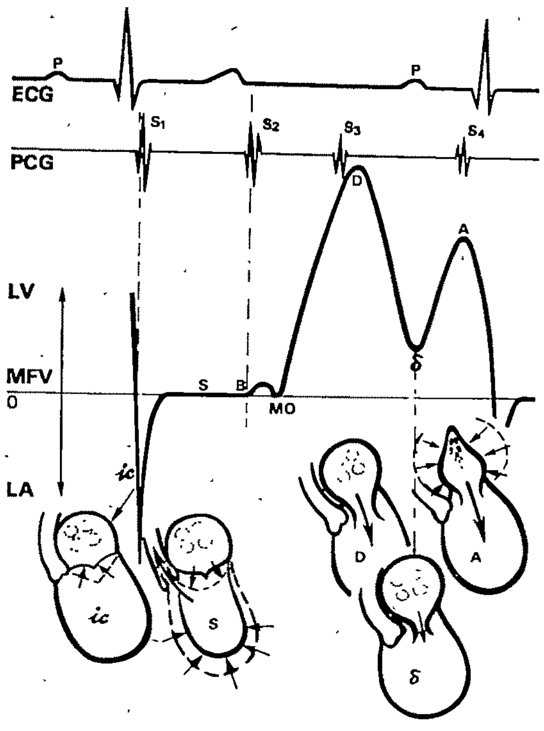

NORMAL MITRAL FLOW VELOCITY PATTERN

FIG. 2 *Physiological interpretation of mitral valve flow velocity curve. Initial negative deflection, ic, is due to bulging of mitral valve into left atrium during isometric contraction provoked by the contraction of papillary muscles and completing apposition of leaflets. Whether it is accompanied by true regurgitation is questionable. S segment along the zero line indicates absence of flow through closed mitral valve. Small segment B-MO extending from notch, synchronous with second heart sound, to onset of D wave delimits isovolumic relaxation period. D wave represents initial diastolic filling of left ventricle, and A wave the end-diastolic filling due to atrial contraction.*

Classification of patients

Patients were classified according to the severity of their stenosis: 1=mild, 2=moderate, and 3=severe. This classification for the pure or predominant lesion on a three-point scale was based partly on the clinical presentation (bedside and *x*-ray examination, electrocardiograph, and clinical course) and on the haemodynamic data (LA-LV pressure gradient and, particularly, a calculated mitral area of greater than 1·5 cm^2 for grade 1, between 1·5 and 1 cm^2 for grade 2, and less than 1 cm^2 for grade 3). The haemodynamic data and classification of patients are shown in Table 1.

For comparison we studied a control group of 11 patients (3 women and 8 men) ranging in age from 25 to 60 years in whom mitral stenosis was ruled out in the course of routine diagnostic catheterization of the left heart. They included four patients with aortic stenosis; two with atrial septal defect, one of whom had a cleft mitral valve; two with chronic pericarditis; and three in whom the chest radiographs were abnormal but who had a normal left heart on catheterization. Diagnostic and haemodynamic data of these patients are summarized in Table 2.

All the patients studied were free from diseases known to modify the isovolumic relaxation period, such as hypertension, moderate to severe aortic or mitral regurgitation, cardiomyopathy, or cardiac failure.

Methods

We used the directional Doppler ultrasonic catheter-tip velocimeter BV 135 Sonicaid (Sonicaid Ltd., Bognor Regis, England) (Kalmanson *et al.*, 1972). The technique of transeptal Doppler ultrasound catheterization of the mitral valve and the physiological interpretation of the recorded curves have been discussed previously (Kalmanson *et al.*, 1975a, b). The mitral flow velocity curves were inscribed on a four-channel 34 or a seven-channel 81 Mingograf direct inkwriting recorder simultaneously with an ECG lead II and a frequency-selected (25, 50, 100, 200, 400, 700 Hz) phonocardiogram at the apex using an EM 22 Elema-Schoenander microphone (chart speed 50 mm/s). The distance between two successive spikes (Fig. 1) equals 1 s.

Patients with mitral stenosis

In all patients with mitral stenosis we determined the following points: A2—the first large high-frequency vibration of the aortic component of the second heart sound, checked by its relationship to the dicrotic notch of the carotid artery pulse tracing; OS—the first large high-frequency vibration of the opening snap sound on the phonocardiogram, checked by its relationship to the O point of the apex cardiogram; MO—the onset on the flow velocity curve of the ascending limb of the initial diastolic filling wave of the left ventricle. We measured the following time intervals: A2-MO—between the first vibration of the aortic second sound and the MO point of the flow velocity curve; MO-OS—between the latter point and the opening snap. Three successive measurements were made for each patient and the average value was retained.

The time lag of the Sonicaid velocimeter has been shown to be about 10 ms (Kalmanson *et al.*, 1972). Therefore a correction of −10 ms was made for the time interval A2-MO, and of +10 ms for the time interval MO-OS. All time intervals were corrected for heart rate according to the Bazett (1920) formula (x $[1/\sqrt{RR}]$).

Control patients

The A2-MO time interval was determined and mea-

TABLE 1 *Classification and haemodynamic data of 15 patients with pure mitral stenosis*

Case No.	*Rhythm*	*LA pressure (mmHg)*	*LV pressure (mmHg)*	*LA-LV pressure gradient*	*Calculated mitral area (cm²)*	*CI (l/min per m²)*	*MS grading*	*Associated lesions*
1	AF	10/4	$106/^{-4}_{+2}$	5·7	1·7	2·6	1	
2	SR	12/7	$200/^{0}_{5}$	2	2·5	2·3	1	
3	SR	17/10	$134/^{-6}_{5}$	3	1·9	2·5	1	Arrhythmias
4	SR	12/2	$97/^{-2}_{+4}$	5	2·3	3	1	
5	SR	20/16	$104/^{-2}_{8}$	11·5	1·1	2·2	2	
6	AF	14/7	$108/^{2}_{8}$	4	1·2	2	2	TS, TR, AS, MR
7	SR	15/8	$122\ ^{0}_{8}$	6·4	1·2	2·4	2	TS
8	AF	25/12	$158/^{0}_{12}$	4	1·6	3·6	2	AS, AI, MR
9	SR	9/4	$93/^{-3}_{3}$	4	1·4	2·9	2	
10	SR	17/5	$134/^{2}_{8}$	3	1·5	2·5	2	
11	SR	20/14	$124/^{-8}_{6}$	9	0·9	2·7	3	
12	SR	22/10	$112/^{-3}_{2}$	11	1·0	2·3	3	
13	AF	35/18	$220/^{0}_{10}$	17	0·4	1·2	3	
14	AF	16/10	$100/^{-2}_{3}$	10	1	2·5	3	AI, MR
15	AF	52/37	$146/^{0}_{6}$	35	0·6	2·4	3	AS

LA=left atrium; LV=left ventricle; CI=cardiac index; MS=mitral stenosis; MR=mitral regurgitation; TS=tricuspid stenosis; TR=tricuspid regurgitation; AS=aortic stenosis; AR=aortic regurgitation; ASD=atrial septal defect.
Conversion from Traditional Units to SI Units: 1 mmHg≈0·133 kPa.

sured with the same correction for heart rate and time lag as for patients with mitral stenosis.

Results

Time relationship between opening snap and mitral valve flow velocity (Fig. 3, 4, 5)

The ascending limb of the initial diastolic filling D wave consistently showed, at a variable height, an isolated notch—that is, a small and brief (0·01 to 0·03 s) downward deflection or plateau synchronous with the opening snap on the phonocardiogram. The onset of this deflection started synchronously with the first vibration of the opening snap and its trough occurred, on average, usually 10 ms later. It was followed, with a variable delay in each patient, by a series of irregular indentations synchronous with the vibrations of the diastolic murmur recorded on the phonocardiogram. The height of occurrence (on the flow velocity trace) of the notch was greater

TABLE 2 *Haemodynamic data of 11 patients in control group*

Case No.	*Mean LA pressure (mmHg)*	*LV pressure (mmHg)*	*LA-LV pressure gradient*	*CI (l/min per m²)*	*Diagnosis*
16	10	$136/^{4}_{8}$	0	3·0	AS
17	5	$160/^{0}_{5}$	0	3·0	AS
18	2	$100/^{0}_{6}$	0	1·7	AS
19	4	$106/^{2}_{4}$	0	3·1	ASD with cleft mitral valve
20	0	$216/^{0}_{4}$	0	4·0	AS
21	8	$108/^{0}_{6}$	0	3·4	Chronic pericarditis
22	2	$125/^{0}_{5}$	0	4·2	Chronic pericarditis
23	4	$110/^{0}_{2}$	0	4·4	Normal heart (abnormal radiograph)
24	3	120/0	0	4·5	ASD
25	4	$120/^{0}_{4}$	0	4·7	Normal heart (abnormal radiograph)
26	4	$126/^{0}_{4}$	0	2·5	Norman heart (abnormal radiograph)

Abbreviations as in Table 1.
Conversion from Traditional Units to SI Units: 1 mmHg≈0·133 kPa.

on the recordings at the centre of the mitral ring than on those at the commissure.

Measurements of A2-OS, A2-MO and MO-OS time intervals and statistical analysis

The normal values of the A2–MO time interval, corrected for time lag and heart rate, are shown in Table 3. They ranged from 0·060 to 0·110 s (mean (±SD) 0·081±0·015).

Patients with mitral stenosis.—The values of A2–OS, A2–MO, and MO–OS time intervals, corrected for time lag and heart rate, are shown in Table 4. A2–OS varied from 0·065 to 0·13 s (mean 0·106±0·019), A2–MO from 0·10 to 0·065 s (mean 0·040±0·019), and MO–OS from 0·055 to 0·075 s (mean 0·066±0·012).

Correlations between values of time intervals and severity of stenosis (Fig. 6, Table 4). A2–OS ranged from 0·12 to 0·13 s (mean 0·125±0·006) for patients with grade 1, 0·09 to 0·13 s (mean 0·108±0·015) for patients with grade 2, and 0·06 to 0·11 s (mean 0·090±0·017) for patients with grade 3 stenosis. A highly significant difference was found between values for grades 1 and 3 (0·01>P>0·001) but a much lesser one between the values for grades 1 and 2 and grades 2 and 3 respectively (0·10>P>0·05). As a whole, the greater the severity of the stenosis the lower the values of A2–OS, including, however, an appreciable overlap between two successive groups. A2–MO ranged from 0·045 to 0·07 s (mean 0·059±0·011) for patients with grade 1, 0·03 to 0·07 s (mean 0·043±0·014) for patients with grade 2, and 0·01 to 0·035 s (mean 0·033±0·017) for patients with grade 3 stenosis. A highly significant difference was found between the values for any two groups (0·010>P>0·001). MO–OS ranged from 0·05 to 0·075 s (mean 0·066±0·011) for patients with grade 1, 0·05 to 0·08 s (mean 0·065±0·012) for patients with grade 2 and 0·055 to 0·085 s (mean

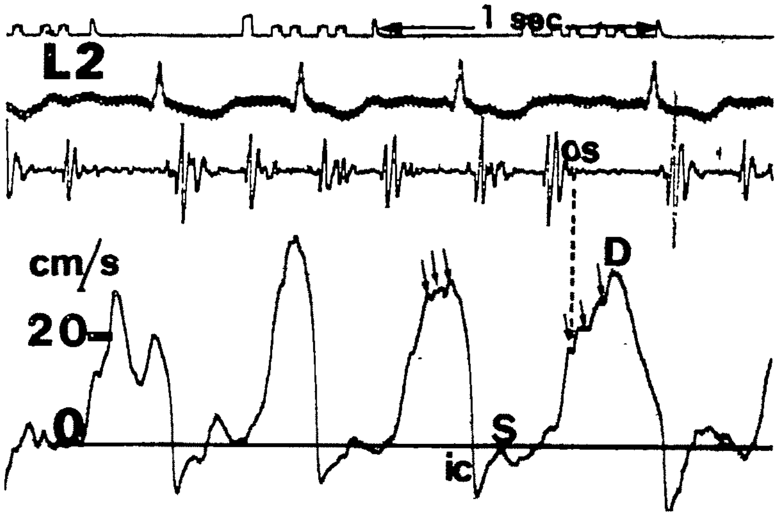

FIG. 3 *Time relationship of opening snap in relation to mitral flow velocity trace in patient with mild stenosis.*

From top to bottom: ECG lead II, phonocardiogram showing heart sounds and opening snap (low frequency band), flow velocity trace. On ascending limb of D filling wave a first notch appears lining up with opening snap on PCG. Trough of notch lines up with first vibration of OS or lags behind an interval of 0·005 to 0·01 s. After notch and at variable distance from it further notches interrupt end of ascending limb of D wave. (ic=isometric contraction deflection. S=systolic flow wave. D=diastolic filling wave.)

0·068±0·13) for patients with grade 3 stenosis, indicating a complete overlap between all three groups (the statistical analysis indeed showed no significant difference).

Correlations between normal values of A2–MO intervals and those of patients with mitral stenosis (Fig 6, Table 4). There was a highly significant difference (P<0·001) between the normal values of A2–MO interval (mean 0·081) and those of all 15 patients with mitral stenosis (mean 0·040 s) of the patients with grade 2 (mean 0·043 s) and of the patients with grade 3 stenosis (mean 0·034 s). The difference was less significant (0·005>P>0·002) between the normal values of A2–MO and those of patients with grade 1 stenosis.

TABLE 3 *Values of A2-MO interval (isovolumic relaxation period) in 11 control patients*

Case No.	*A2-MO (s)*
16	0·080
17	0·060
18	0·080
19	0·060
20	0·065
21	0 090
22	0·090
23	0·110
24	0·090
25	0·075
26	0·090

Correlations between values of MO-OS interval and presence or absence of mitral calcification (Table 5). The nine patients with calcification of the mitral valve had a mean value of A2–MO interval of 0·073±0·008 s, whereas those without calcification had a mean value of 0·056±0·008 s, indicating a highly significant difference (P<0·001).

Discussion

Genesis of mitral opening snap

Attempts to explain the genesis of the opening snap (OS) have established its time relationship with myocardial events, using the jugular venogram and apex cardiogram, and with valve movements, using the echocardiogram of the anterior leaflet or angiograms. The recent advent of mitral flow

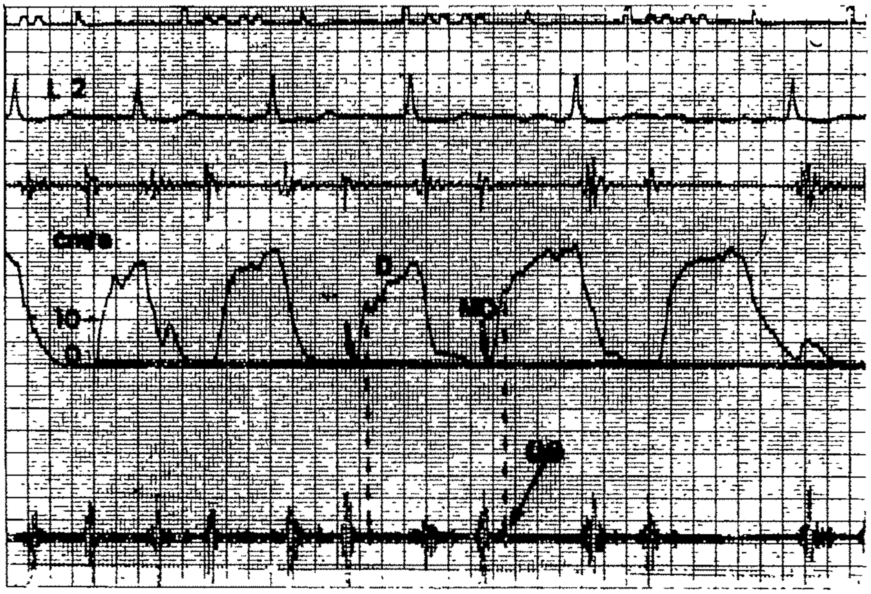

FIG. 4 *Time relationship of mitral opening snap with respect to mitral valve flow velocity trace in patient with severe mitral stenosis and atrial fibrillation.*

From top to bottom: ECG lead II, phonocardiogram showing heart sounds and opening snap (low frequency band), flow velocity trace, additional high frequency band phonocardiogram. MO=mitral opening point (onset of diastolic filling wave D). The ascending limb of D wave is interrupted by first notch and thereafter has lesser slope with further small indentations. The summit of notch coincides with first vibration of opening snap, and its trough lags behind by an interval of 0·05 to 0·15 s.

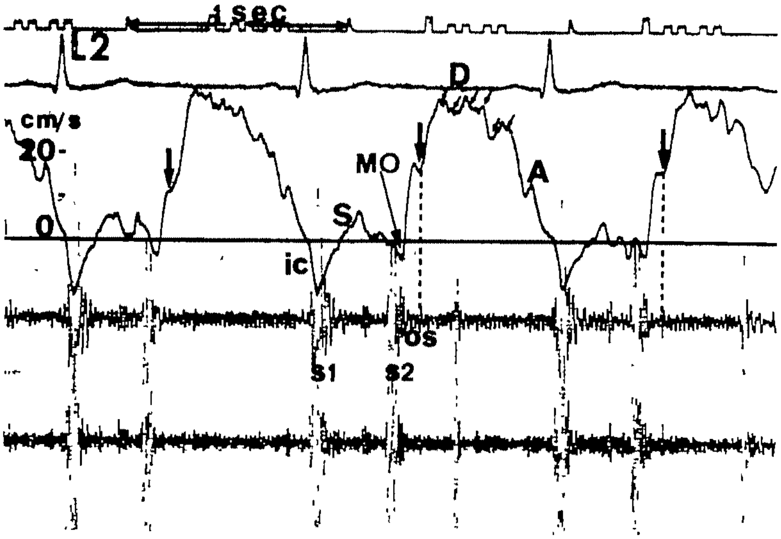

FIG. 5 *Time relationship of mitral opening snap with respect to mitral valve flow velocity trace in a patient with mild stenosis in sinus rhythm. S1=first heart sound. S2=second heart sound. OS=opening snap. Opening snap lines up with notch interrupting the ascending limb of D wave. Trough of notch occurs 0·10 s after first vibration of snap.*

TABLE 4 *Values of A2-OS, A2-MO, and MO-OS time intervals, corrected for time lag and heart rate, correlated with severity of stenosis and presence of mitral calcification in 15 patients with mitral stenosis*

Case No.	*Rhythm*	*Mean A2-OS (s)*	*Group mean*	*Mean A2-MO (s)*	*Group mean*	*Mean MO-OS (s)*	*Group mean*	*Calcification*	*Grading of severity*
1	AF	0·13	0·125 ±0·006	0·055	0·059 ±0·011	0·075	0·066 ±0·011	+	1
2	AF	0·12		0·07		0·05		0	
3	SR	0·12		0·045		0·075		+	
4	SR	0·13		0·065		0·065		0	
5	AF	0·09	0·108 ±0·015	0·035	0·043 ±0·014	0·055	0·065 ±0·012	0	2
6	AF	0·12		0·04		0·08		+	
7	SR	0·10		0·050		0·050		0	
8	AF	0·11		0·035		0·075		+	
9	AF	0·13		0·07		0·06		0	
10	AF	0·10		0·03		0·07		+	
11	AF	0·11	0·090 ±0·017	0·025	0·033 ±0·017	0·085	0·068 ±0·013	+	3
12	SR	0·085		0·010		0·075		+	
13	AF	0·10		0·03		0·07		+	
14	AF	0·09		0·035		0·055		+	
15	SR	0·065		0·01		0·055		0	

AF=atrial fibrillation; SR=sinus rhythm. Grading of severity of stenosis: 1=mild; 2=moderate; 3=severe.

TABLE 5 *Correlations between MO-OS interval and presence or absence of mitral calcification in 15 patients*

Case No.	*Mitral calcification*	*MO-OS (s)*	*Mean MO-OS*
1	+	0·075	
3	+	0·075	
6	+	0·08	
8	+	0·075	
10	+	0·07	0·073±0·008
11	+	0·085	
12	+	0·075	
13	+	0·07	
14	+	0·055	P<0·001
2	—	0·05	
4	—	0·065	
5	—	0·055	
7	—	0·050	0·056±0·006
9	—	0·06	
15	—	0·055	

velocity recording by transeptal Doppler ultrasound catheterization of the left heart cavities has provided a new technique for relating phonocardiographic events of the left heart, in particular the mitral opening snap, to instantaneous mitral flow phenomena. The validity of such time relationships quite obviously relies on the accuracy of phonocardiographic and velocimetric determinations. It is therefore appropriate firstly to discuss our technique.

The differentiation of the OS from the pulmonary component of the second heart sound could be easily ascertained by the wide A2–OS interval, which ranged from 0·08 to 0·13 s. In none of the patients was there a right bundle-branch block sufficient to cause such a delay. Even in patients with an A2–OS interval of 0·10 to 0·13 s the confusion with a third heart sound could be avoided by checking the close time relation of the snap with the O point of the apex cardiogram. Incidentally, the OS always occurred well before the

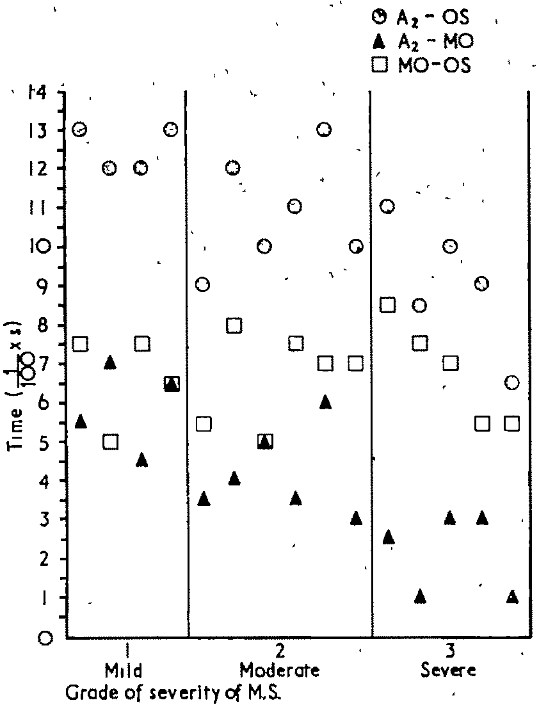

FIG. 6 *Diagrammatic relationship between values of A2-OS, A2-MO, and MO-OS time intervals with grading of severity of stenosis. Values of A2-OS clearly decrease with increasing severity of stenosis. However, there is appreciable overlap between groups 1 and 2 and groups 2 and 3. Groups 1 and 3 and groups 2 and 3 are distinct for values of A2-MO but a small overlap exists between groups 1 and 2. There is complete overlap between all groups for MO-OS values.*

peak of the diastolic initial filling D wave of the left ventricle. Since the transmission delay of the phonocardiograph is negligible, determination of A2 and OS could be considered as accurate to within ±5 ms.

Yellin and Laniado (Laniado *et al.*, 1973; Yellin *et al.*, 1976) experimentally recording phasic mitral valve flow by means of an electromagnetic cuff flowmeter simultaneously with left atrial and ventricular pressures, demonstrated that the point of crossover of the atrial and ventricular pressure curves was synchronous with the onset of the filling flow wave of the left ventricle—that is, with the beginning of mitral valve opening. Similarly the onset of the velocity flow curve in early diastole may also be considered as representing the true opening of the valve. However, since the transmission delay of the Sonicaid BV 135 velocimeter is about 10 ms (Kalmanson *et al.*, 1972) a correction for this time lag must be made in assessing the timing of the MO point. Accuracy of such a determination may therefore be considered as being within the range of observer's error—that is ±5 ms.

The results of our study allow us to draw the following conclusions.

1) The so-called mitral opening snap occurs after true mitral valve opening, a view expressed long ago (Bouillaud, 1835; Tavel *et al.*, 1965; Fishleder, 1966).

2) The mitral opening snap occurs at a time when the transmitral flow velocity (and consequently also flow rate) has already reached a finite value, and this value is usually well below the peak velocity of the filling wave. This indicates that the opening snap takes place when blood has already begun to flow through the valve—a fact that was denied by Ross *et al.* (1961), whose cineangiograms failed to disclose any leakage of contrast material through the valve before the OS. The finding that the flow velocity increases steadily before and after the opening notch (ON) shows that the valve is open at the time of the snap and remains open afterwards. This rules out the possibility of a sudden closing of the valve being the origin of the sound, as Rodbard and Libanoff (1972) suggested.

3) The very pattern of the notch (downward deflection or small plateau) synchronous with the OS indicates that blood flow passing through the valve is for a very brief period *slowed down* (the velocity decreases or ceases to increase), and thereafter continues to increase. Our finding of a brief, transient slowing down of the flow velocity suggests that the latter is most likely to be due to a transient upward displacement of the leaflets towards the left atrium, as if they were suddenly halted by an abrupt tensing of the chordae tendineae—a mechanism in keeping with the general opinion that the opening snap is produced by the sudden tensing of the chordae tendineae at the time of complete excursion of the leaflets. Our observations provide the haemodynamic counterpart of the demonstrations offered previously by studies of mitral valve movements (Ross *et al.*, 1961; McCall and Price, 1967; Friedman, 1970; Millward *et al.*, 1973). These authors concluded that the opening snap occurred at almost exactly the time of total excursion of the valve in patients with mitral stenosis or in situations associated with excess flow passing through the mitral valve.

4) The sound turns out to be a 'tensing' or 'tension' snap rather than a true 'opening' snap, and surely not a 'closing' sound.

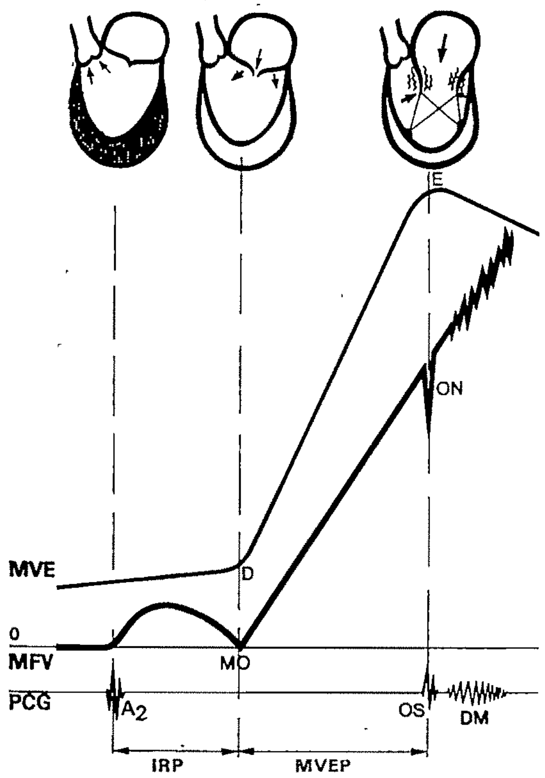

FIG. 7 *Schematic early diastolic time relationship between opening snap, echo tracing, and flow velocity curve of mitral valve in patients with mitral stenosis. A2-OS interval is the sum of following two successive components: A2-MO, or true isovolumic relaxation period, and MO-OS, or excursion time of the valve. A2-MO is affected by severity of stenosis (the more severe the latter the shorter A2-MO), whereas MO-OS is essentially influenced by presence of calcification, which increases its duration.*

Analysis and significance of A2-OS interval. A further finding of our study was that the A2–OS interval does not—even approximately—represent the true isovolumic diastolic relaxation period. Neither does the time interval between A2 and the O point of the apex cardiogram, which either coincides with or lags behind the OS. In fact, the A2–OS interval consists of the sum of two component intervals (Fig. 7)—namely, the A2–MO, extending from the aortic component of the second heart sound to the time of the MO point on the flow velocity curve, and the MO–OS, extending from the latter point to the time of the opening snap on the phonocardiogram. Since the MO point represents the true beginning of the mitral valve opening, the A2–MO interval can be considered as covering fairly well the true isovolumic relaxation period (IRP) of the left ventricle, and the MO–OS interval as reflecting accurately the time required for the valve leaflets to complete their full excursion from the onset of the valve opening (mitral valve excursion period, MVEP). In fact, the true physiological isovolumic relaxation period (IRP) starts before the aortic closure, and, more precisely, for Wiggers (1952) at the steepening point of the decline of the ventricular pressure curve prior to the trough of the aortic incisura. On the other hand, the aortic component (A2) of the second heart sound does not coincide with the aortic closure but precedes it by as much as 10 to 20 ms (McCanon, Arevalo, and Meyer, 1964). Finally, the error made by assuming A2 to be the starting point of the IRP may be held to be negligible, and it seems legitimate to consider for clinical purposes that A2–MO represents fairly well the IRP. Not only are the two component intervals clearly distinct in timing but our data further substantiate that their value may vary in relation to the severity of the stenosis or the presence or absence of mitral calcification, thereby inferring that their determining factors are at least partly different.

Normal values and factors in variation of A2-MO time interval (IRP). Arevalo and Sakamoto (1964) measured in 30 patients with a normal left heart the time interval extending from A2 to the point of crossover of the left atrial and ventricular pressures. The values ranged from 0·55 to 0·120 s (mean 0·81 s). These are in keeping with our results—0·060 to 0·110 s (mean 0·081 s) after correction for heart rate—but at some variance from those of Nimura determined by the external Doppler technique—mean 0·067 s ±0·011 (Nimura *et al.*, 1968). Furthermore, Weisfeldt *et al.* (1974), using a right heart bypass preparation in normal dogs, studied the effects of heart rate, stroke volume, and arterial pressure on the duration of the isovolumic diastole. They showed that the latter was shortened by a larger stroke volume due to the rise in left atrial pressure, and insignificantly decreased at higher heart rates with constant stroke volume. In our patients with mitral stenosis, in whom stroke volume, heart rate, and arterial pressure were interdependent, we found that the A2–MO time interval corrected for heart rate decreased with increasing severity of the stenosis (Table 4)—a finding consistent with the well-known earlier occurrence of the point of crossover of the left atrial and left ventricular pressure curves with increasing severity of the mitral stenosis. Furthermore, and though our small series of investigations requires confirmation on a larger number of patients, the statistical analysis is in favour of a higher reliability for the A2–MO versus the A2–OS values in assessing the severity of the stenosis ($0{\cdot}01 > P > 0{\cdot}001$ versus $0{\cdot}10\,P > 0{\cdot}05$ for the two successive grades 1 and 2, and 2 and 3).

Factors in variation of MO-OS time interval (MVEP). Table 4 shows the lack of correlation between the MO–OS time interval and the severity of the stenosis. Table 5, on the other hand, shows that when mitral calcification is present, the interval is longer. Conversely, when there is no calcification the MO–OS is shorter. These findings are consistent with Edler's on the value of the speed of the upstroke DE on the echocardiogram of the anterior leaflet (Fig. 6) (Edler, 1967). In a series of 130 patients with mitral valve stenosis, Edler showed that the average speed of upstroke as measured on the segment DE of the echocardiogram was 423 mm/s in patients without calcification and 174 mm/s in patients with much calcification. Since the speed of upstroke is inversely proportional to the duration of the MO–OS interval (duration of excursion of the valve), both studies show that the presence of calcification slows down the velocity of valve opening.

Factors in variation of A2-OS time interval. We can infer from the preceding considerations that the A2–OS time interval is in fact the sum of successively the true isovolumic relaxation period and the mitral valve excursion period. It extends from the onset of the aortic valve closure to the completion of the mitral valve opening in patients with mitral valve disease. In such patients its duration depends on various and complexly interrelated factors, as Weissfeldt has shown—namely, stroke volume, heart rate, arterial pressure—and also on the severity of the stenosis and the presence or absence of calcification. The complexity of these interwoven factors, and in particular the fact, which appears from our data, that they may vary in their effect in the same patient, may largely explain the conflicting statements about the clinical value of the A2-OS interval in mitral stenosis. For example, a severe stenosis with much calcification will be associated with shorter A2-MO interval which is compensated, however, by a longer MO-OS interval. The resulting A2-OS interval will therefore be longer than might be expected from the severity of the stenosis. In other words, the A2-OS interval is related to the severity of the mitral stenosis but it is influenced by so many other factors that a clinical interpretation of it should be made with great caution. These factors must be investigated further before the A2-OS time interval can be used as a reliable index of the severity of mitral valve disease.

Conclusions

The following conclusions may be drawn from our study.

1) The mitral opening snap occurs only when the valve cusps have completed their full opening excursion. Since the valve cusps take a finite time to open there has been a significant flow through the valve before the opening snap occurs. It corresponds to a small, transient slowing down of the mitral flow velocity.

2) Our findings support the hypothesis of a sudden tensing of the valve abruptly stretched by its chordae tendineae at the time of maximum excursion of the leaflets.

3) The classical A2-OS interval is composed of two successive intervals—the A2-MO, synchronous with the isovolumic relaxation period, followed by the MO-OS, or excursion time of the valve cusps.

4) Both the A2-OS and A2-MO intervals are approximate indexes of the severity of the stenosis, but the A2-MO is the more reliable. On the other hand, the MO-OS interval is irrelevant to the severity of the stenosis and is essentially affected by the presence of mitral calcification, which increases the inertia of the valve cusps.

5) Our analysis of the A2-OS interval and of its components allows us to state that it is essentially different from other intervals such as the isovolumic relaxation period and the A2-O, O being the lowest point of the apex cardiogram. Apparent close relationships between these different intervals in patients with mitral valve stenosis are therefore purely coincidental. Our findings and the great complexity of the factors that determine the different time intervals explain the conflicting statements in the literature about the reliability of these intervals in assessing the severity of mitral stenosis. The greatest caution in their clinical interpretation is called for.

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The natural history of rheumatic aortic regurgitation and the indications for surgery[1]

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A detailed review was made of 180 patients with severe aortic regurgitation of rheumatic origin. Of these patients, 110 underwent aortic valve replacement. Thirty-nine clinical and haemodynamic factors were studied in an attempt to define those associated with (1) death before surgery, (2) a higher incidence of complications and hospital mortality after surgery, and (3) an unsatisfactory longer-term result after surgery. Only heart failure, radiographic heart size, left ventricular hypertrophy, and ventricular premature beats were associated with death before surgery. No factor predisposed to surgical complications and only preoperative factors associated with an unfavourable result after surgery were advanced heart failure, cardiomyopathy, extreme cardiomegaly, and ventricular premature beats.

It is concluded that the indications for operation are: a cardiothoracic ratio of greater than 0·60, or a history of heart failure combined with electrocardiographic evidence of extreme left ventricular hypertrophy. Operation may be safely postponed if these indications are not met, though the presence of ventricular extrasystoles or evidence of independent myocardial disease are further factors which should influence the decision.

New Zealand has a relatively isolated community and a high incidence of rheumatic fever, especially among its Maori and Pacific Island people (New Zealand Department of Statistics, 1974) and provides favourable conditions for a study of the natural history of rheumatic heart disease. This fact, together with uncertainty about the indications for surgery in patients with well-compensated aortic regurgitation, prompted us to reinvestigate the indications for surgical intervention in this disease.

Valve surgery is indicated when the risk of operation is less than the risk of postponement. The latter risk includes:

1) death without operation
2) progression to the point where the risk of operation is excessive, and
3) progression to the point where the long-term result will be unsatisfactory despite good surgery.

In the present study, we have examined these factors in an effort to define more clearly the place of aortic valve replacement in the treatment of severe aortic regurgitation.

Subjects and methods

One hundred and eighty patients with severe aortic regurgitation of rheumatic origin referred to Green Lane Hospital from 1958 to 1967 were assessed. A history of rheumatic fever was definite in 145 patients and probable in the remaining 35 patients. The diagnosis of aortic regurgitation was obvious clinically and there was rarely any doubt about severity though this was difficult to define in quantitative terms (Judge and Kennedy, 1970). In 167 patients, the diastolic pressure was less than 60 mmHg (8·0 kPa), with a pulse pressure greater than 50 per cent of the systolic pressure. A further 13 patients were included with a diastolic pressure greater than 60 mmHg (8·0 kPa), where the findings were consistent with severe aortic regurgitation, usually with heart failure. Data from catheterization were available in 13 patients, but added little to the clinical assessment. The series does not include any patients with associated mitral or tricuspid disease unless the lesion was mild. Fifty-three patients with moderate aortic regurgitation of non-rheumatic aetiology referred during the same period were also excluded from the study. A review was made of all available past records from medical practitioners and hospitals, including chest radiographs and electrocardiograms. Further information was obtained from patients and relatives. The information collected was recorded on punch cards and analysis was restricted to data recorded with confidence. The influence of the 39 preoperative factors listed in Table 1 was examined

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TABLE 1 *Preoperative factors examined*

1–3	Age, sex, and race
4	Period of observation
5	Time since last review
6	Bacterial endocarditis
7	Age at the first attack of rheumatic fever
8	Number of attacks of rheumatic fever
9	Time interval from first attack of rheumatic fever to onset of symptoms
10	Time interval from first attack of rheumatic fever to assessment
11	Mode of onset of aortic regurgitation (acute or chronic)
12	Duration of significant aortic regurgitation
13	Presence of a mild mitral valve lesion
14	Presence of mild aortic stenosis
15	Presence of cardiomyopathy
16	Presence of systemic hypertension
17	Presence of coronary heart disease
18–20	Angina at rest or on effort or both
21	Duration of dyspnoea
22–24	An episode of paroxysmal nocturnal dyspnoea, orthopnoea, or frank congestive heart failure
25–26	Treatment with digitalis or diuretics
27–29	Systolic, diastolic, and pulse pressure
30–32	Initial, final, and increase in CTR
	Electrocardiographic abnormalities:
33	i Rhythm disturbances
34	ii Frontal plane axis
34	iii Infarct pattern
35	iv Fascicular block
36–37	v Bundle-branch block (left and right)
38–39	vi Degree and duration of left ventricular hypertrophy

in relation to outcome. If a relation between a factor and survival or clinical status became evident, the significance was tested by analysing the difference between two binomial proportions (Goldstein, 1964).

Of the 180 patients studied 22 died, 48 remained under observation throughout the review period, and 110 were subjected to aortic valve replacement. The mean follow-up period for each group was 2·3 years, 3·7 years, and 2·3 years, respectively. It is obvious that the operated patients differed from the other groups in that they had survived to the point where their disease was considered severe enough to warrant valve surgery. In order to obtain an overall view of the way in which the 39 factors studied influenced patient survival it was necessary to consider the 180 patients as a composite group.

A. Factors contributing to death before operation

For this part of the study comparisons were drawn between patients who died before operation, and those who survived either to operation, or without the need for surgery. The time of assessment was taken as the last clinic attendance before death for those who died. Patients submitted for operation were assessed immediately beforehand (the period of observation for this part of the study thus ending at this point), while others were assessed after their last clinic attendance.

B. Factors associated with a higher incidence of surgical complications in patients who came to operation

All 110 operated patients underwent aortic homograft valve replacement (Barratt-Boyes, 1965). Surgical complications were defined as significant residual aortic regurgitation, myocardial damage, conduction defect, or any combination of these following operation. The incidence of each of the 39 factors studied was recorded in patients who suffered surgical complications and compared with the incidence in those who had an uneventful operation. The surgical complication rate does not reflect current results as the study concerns the early period of homograft replacement from 1962 to 1968.

C. Preoperative factors associated with unsatisfactory longer-term result after good operation

Surviving patients were assessed at an average of 2·7 years after operation, the minimum follow-up period being 1 year and the maximum period 4 years. The longer-term result was classified as good if patients were in NYHA (1964) Class I or II with reduction of the radiographic cardiothoracic ratio (CTR) to less than 0·55. The result was classed as satisfactory if patients were in Class I or II, with a reduction in radiographic heart size but with a CTR of greater than 0·55. Other surviving were classed as poor. Late deaths were defined as those occurring after discharge from hospital.

The incidence of each of the 39 preoperative factors was compared in each group—good, satisfactory, poor, late death—in the 76 patients who had entirely satisfactory operations. Exclusion of patients in whom a surgical complication occurred was necessary to permit patients proper assessment of the influence of preoperative factors.

Results

A. Factors contributing to death before operation

One hundred and ten were followed until surgery, 22 died without operation, and 48 were still being managed conservatively at the time of assessment. The incidence of each factor studied was compared in the group of 22 patients who died, with the incidence in the 158 who survived to the time of assessment.

The symptomatic class of the 158 patients alive at the time of assessment (New York Heart Association, 1964) was as follows: Class I—42, Class II—60, Class III or IV—56.

There were only 4 factors from among the 39 studied which were related to the death of patients while under observation. These were heart failure, the size of the heart, the presence of extreme left ventricular hypertrophy, and cardiac arrhythmias (Fig. 1).

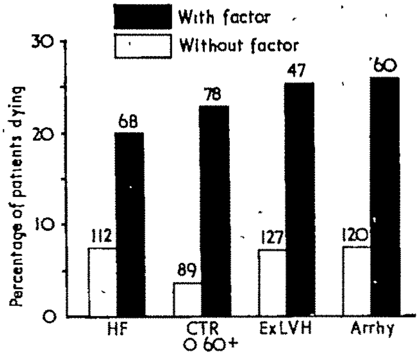

FIG. 1 *The effects of heart failure (HF), cardiothoracic ratio greater than 0·60 (CTR 0·60+), extreme left ventricular hypertrophy (ExLVH), and arrhythmias (Arrhy) on the death rate without surgical intervention. The histograms show the death rate in the groups of patients with and without each factor. The numbers shown are the total number of patients in each group.*

TABLE 2 *Criteria of left ventricular hypertrophy*

Voltage				*T wave in chest chest leads*
	S_{V1}	$+$	R_{V5}	
		or		
	S_{V2}		R_{V6}	
Mild	35	—	60 mm	Normal
Moderate	i:	>	60 mm	Normal
or	ii:		35–60 mm	Reduced/flat/biphasic
Severe		—		0–2·9 mm (inversion)
Extreme		—		3 mm < (inversion)

1. Heart failure For the purpose of this study a patient was said to have heart failure if at any time he had an episode of paroxysmal dyspnoea (51 patients), or orthopnoea (62 patients), or congestive heart failure (30 patients). Most patients with heart failure responded to medical treatment and there was no statistical difference in the death rate of patients in these three categories during the period of observation. The categories were, therefore, grouped together, a total of 68 patients being involved. (As noted below, however, the presence of severe congestive heart failure at the time of operation was related to an unfavourable outcome in individual cases.)

This history of an episode of heart failure was related to an increased death rate. Fourteen of 68 (21%) patients with heart failure died, compared with 8 of 112 patients (7%) without heart failure ($0{\cdot}001 < P < 0{\cdot}01$; Fig. 1), but most of these 14 patients also showed other unfavourable features. There were no deaths in 13 patients with heart failure but without cardiac enlargement ($CTR > 0{\cdot}60$), extreme left ventricular hypertrophy, or arrhythmia.

2. Heart size This was assessed radiologically by the cardiothoracic ratio (CTR) defined as the ratio of heart and internal chest diameter on a 6-foot posteroanterior chest *x*-ray. Patients who had only anteroposterior *x*-rays were not included. Eighteen of 78 patients (23%) with a CTR greater than 0·60 died, compared with 3 of 89 patients (3%) with a CTR less than 0·60 ($0{\cdot}001$ $P < 0{\cdot}01$; Fig. 1). Of these latter 3, one died 3 years after being seen and no details of the death are known, but he may have had an enlarged heart at the time of death. The second patient who had a CTR of 0·50, with first degree heart block and ventricular premature beats, died 8 months after being seen. At necropsy, his heart was enlarged (weight 832 g), with gross hypertrophy of the left ventricle. A third patient had a CTR of 0·59 with extreme left ventricular hypertrophy and ventricular premature beats. There were, therefore, unusual features about each of these 3 patients and 'unexpected death' was exceptional in patients with a CTR of less than 0·60.

Twenty-three patients had a CTR more than 0·60 without heart failure, extreme left ventricular hypertrophy, or arrhythmia and 2 of these patients died.

3. Left ventricular hypertrophy An arbitrary assessment of left ventricular hypertrophy was used, based on voltage and T wave changes as set out in Table 2. Modification was necessary in patients taking digitalis, usually by subtracting 1 grade unless the diagnosis of extreme left ventricular hypertrophy was obvious.

No patient with mild or absent left ventricular hypertrophy died, 9 of 110 patients (8%) with moderate or severe left ventricular hypertrophy died compared with 12 of 47 patients (26%) with extreme left ventricular hypertrophy ($0{\cdot}001 < P < 0{\cdot}01$; Fig. 1). However, 6 of the 12 patients had the other 3 factors as well, 4 had heart failure plus a second factor and 2 had one other factor. No patient dying had extreme left ventricular hypertrophy only. Similar considerations applied to patients with severe or moderate left ventricular hypertrophy and it appeared that this affected death rate only in the presence of other factors.

4. Arrhythmias These were recorded in 60 patients (Table 3) and included first degree heart block (24), ventricular premature beats (22), first degree heart block plus ventricular premature beats (7), atrial fibrillation (6), and atrial fibrillation plus ventricular premature beats (1).

Thirteen of the 60 patients (22%) with arrhythmias died compared with 9 of 120 patients (8%) in sinus rhythm ($0\cdot001 < P < 0\cdot01$: Fig. 1). This difference was mainly because of the presence of ventricular premature beats. An arrhythmia was the least important of the 4 factors studied but became significant when other factors were also present. Thus, only 2 of 10 patients with heart failure, an enlarged heart, extreme left ventricular hypertrophy, and sinus rhythm died, while 6 of 12 patients with those 3 factors plus ventricular premature beats died. (It is possible, however, that an unrecorded rhythm abnormality was the immediate cause of death in 6 patients dying without heart failure.)

Other factors studied

Seventy-five per cent of patients were male, but men and women tolerated the disease equally. Thirty-one per cent were of Polynesian descent compared with 6 per cent in a parallel study of patients with aortic regurgitation of non-rheumatic origin. Contrary to the experience in patients with multiple valve disease, all races tolerated the disease equally.

Eighty per cent of patients had had their first attack of rheumatic fever between the ages of 5 and 15 years. The influence of time since the first attack could not be separated from the effect of age and neither was related to death rate. Multiple attacks of rheumatic fever had no discernible effect on outcome, but it is likely that many patients with multiple attacks developed multiple lesions and were, therefore, excluded from the study.

It was not possible to extract reliable information about the duration of severe aortic regurgitation but the duration of significant regurgitation was known in 113 patients, it being considered significant when it produced obvious haemodynamic effects. Unexpectedly, outcome did not relate to this.

Bacterial endocarditis had occurred in 31 patients. This complication led to surgery in 26 cases, but with the infection fully treated there was no other difference between these patients and those who had not had bacterial endocarditis. Fifteen patients were regarded as having an acute onset or acute deterioration of aortic regurgitation not caused by bacterial endocarditis. There was no difference in the subsequent behaviour of this group compared with that of patients with a more gradual onset.

The death rate of patients with angina at rest or on effort (6/39) was not significantly different from the death rate in patients without angina (16/141). Coronary heart disease was diagnosed clinically in 8 patients, but the numbers were insufficient for analysis. Coronary arteriograms were not performed in the assessment of patients with aortic regurgitation during the period of this study. Neither left axis deviation nor fascicular block in the electrocardiogram was related to an increased death rate.

A diagnosis of 'cardiomyopathy' was made in 6 patients with evidence of important mycocardial dysfunction. This difficult diagnosis was made preoperatively in the presence of gross cardiomegaly or haemodynamic abnormality not explained by the valve lesion alone. Of 27 patients with CTR more than 0·65, 6 were considered to have cardiomyopathy. The aetiology was active rheumatic fever in 1 patient, diabetes and hypertension in 1, and advanced decompensated valvular disease in 4 patients. All survived to undergo surgery. Eight patients with systemic hypertension behaved no differently from others without hypertension, but the numbers were too small for proper comparison.

Symptomatic status

Six objective measurements correlated closely with symptomatic status at the time of review (Table 3), and there was a high level of association between many of these factors. Thus patients with large hearts tended to be those with heart failure and extreme left ventricular hypertrophy.

TABLE 3 *Percentage of patients in each symptomatic class with significant objective factor*

	Symptomatic class			*Significance*		
Factor	*I*	*II*	*III and IV*	*P : I v II*	*P : I v III and IV*	*P : II v III and IV*
CTR > 60	20	42	57	<0·05	<0·001	NS
Arrhythmia	5	37	41	<0·005	<0·001	NS
Extr. LVH	7	27	28	<0·005	<0·005	NS
LAD	7	30	50	<0·01	<0·0001	<0·01
Fasc. block	4	12	13	NS	<0·01	NS
Age >40 yr	2	22	45	<0·01	<0·0001	<0·01

CTR=cardiothoracic ratio Extr. LVH=extreme left ventricular hypertrophy
LAD=left axis deviation Fasc. block=fascicular block
P: I v II etc.: probability that difference between I and II, etc. occurred by chance

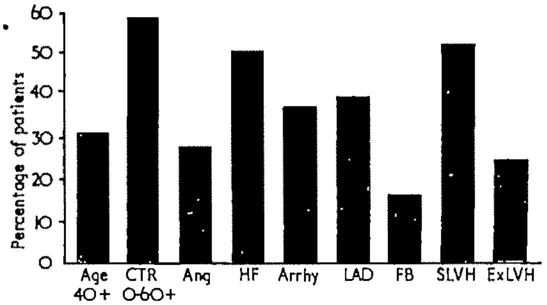

FIG. 2 *The incidence in patients coming to surgery of the factors which were found to affect symptomatic status. CTR 0·60+ = cardiothoracic ratio greater than 0·60; Ang = angina; HF = heart failure; Arrhy = arrhythmia; LAD = left axis deviation; FB = fascicular block; SLVH = severe left ventricular hypertrophy; ExLVH = extreme left ventricular hypertrophy.*

B. Factors associated with higher incidence of surgical complications in patients who came to operation

One hundred and ten patients underwent aortic homograft replacement after a period of observation of 0 to 12 years (mean 2·3). The major clinical features of these patients are illustrated in Fig. 2. At the time of operation 10 were in Class I, 44 in Class II, and 56 were in Class III or IV.

Thirty-four patients developed surgical complications. These include myocardial damage (9 cases), significant aortic regurgitation soon after operation (16), myocardial damage plus aortic regurgitation (2), a conduction defect (1), a conduction defect plus aortic regurgitation (1), and hospital deaths (4).

Three of the 39 factors studied were associated with a higher surgical complication rate. These were: heart failure, a CTR more than 0·65, and the presence of a mitral lesion which had been considered minor. Changes in surgical technique can, however, account for the apparent influence of each of these factors. In December 1964, the surgical technique was modified by tailoring the aortic root when necessary to ensure a better fit of the donor valve (Barratt-Boyes and Roche, 1969). This resulted in a lower incidence of early homograft valve regurgitation. From about the same time, fewer patients were seen with end-stage disease, so that fewer patients had pronounced cardiomegaly or heart failure (78% before, compared with 40% after).

The association of a higher surgical complication rate with minor mitral valve disease was unexplained, though mitral valve lesions were also more common in the early period. It appeared, therefore, that the relation of surgical complication rate with these 3 factors was spurious, and that surgical complications in this series were independent of preoperative status.

The 34 patients with an unsatisfactory operation were also assessed in regard to their symptomatic result. Four were good, 4 satisfactory, and 10 poor. There were 15 deaths (4 hospital and 11 late) and 1 patient was lost to follow-up.

Hospital deaths One patient (aged 13 years) had an emergency operation for terminal heart failure. Cardiac arrest occurred during the anaesthetic induction and he did not survive operation. The other 3 patients all died from surgical complications.

Late deaths Seven of the late deaths were related to homograft valve failure, caused either by cusp rupture, perivalvular suture line leak, or bacterial endocarditis. Preoperative factors may have played a role in the other 4 patients. One had congestive heart failure with angina, one cardiomyopathy, one extreme cardiomegaly (CTR = 0·75), and one frequent ventricular premature beats.

C. Preoperative factors associated with unsatisfactory longer-term result after good operation

Seventy-six patients underwent an entirely satisfactory operation. The symptomatic result over a period of 1 to 3 years was good in 51 patients and satisfactory in 14. One patient with cardiomyopathy had persistent cardiomegaly despite successful surgery and was classified as a poor result. There were 8 late deaths in this group from 4 to 36 months after surgery and 2 further patients were lost to follow-up. Two late deaths resulted from bacterial endocarditis, but preoperative factors were thought to have contributed to the outcome in the other 6 patients. Two of these had a cardiomyopathy, 1 had cardiomegaly (CTR = 0·78), and 2 underwent surgery in extreme heart failure. The final patient had had frequent ventricular premature beats preoperatively.

Cardiomyopathy, which was present in 6 patients before operation, appeared to be an important factor, which adversely influenced the long-term result. Three of these had entirely satisfactory operations but all did poorly. Two died and 1 had a poor long-term result. Cardiomegaly (CTR >0·65) was present in 8 patients who had a satisfactory operation. Three of these subsequently died and are compared with 4 deaths among 62 patients with a CTR of less than 0·65. Striking cardiomegaly thus appeared to be associated with a poorer longer-term result.

Four of 26 patients with a rhythm abnormality before operation died, and are compared with 4 deaths in 50 patients who had sinus rhythm. Rhythm abnormalities were more commonly associated with cardiomegaly and congestive heart failure, so that they did not appear to be important in themselves though they may have contributed to late death in some cases.

There was no evidence that preoperative angina had a deleterious effect. Of 31 patients with angina who underwent surgery, 26 had additional unfavourable features, but 27 of the 31 patients were well and free from angina after operation: the remaining 4 died late. One (who had an unsatisfactory operation) also had considerable congestive heart failure preoperatively, one had pronounced cardiomegaly (CTR=0·75), one had a cardiomyopathy, and one had frequent ventricular premature beats.

In summary, preoperative cardiomyopathy, a distinct degree of cardiomegaly (CTR>0·65), congestive heart failure at the time of operation, and ventricular premature beats were all associated with a poor longer-term result after satisfactory surgery, and probably contributed to poor results after satisfactory surgery. There was no evidence that preoperative angina, paroxysmal dyspnoea, or orthopnoea without persistent congestive heart failure had a deleterious effect on the longer-term result.

Discussion

A variable prognosis in patients with severe aortic regurgitation is well known and it is clearly important to establish logical criteria for operative intervention. This study has limitations inherent in all retrospective surveys, but nevertheless accurate historical data were obtained from a large number of patients. The development of surgical techniques for aortic valve replacement in the middle of the period under review limited its value as a study of the natural history of the untreated disease but allowed for an assessment of the influence of preoperative factors on postoperative outcome. Eight patients died before the advent of surgery and a number of patients had end-stage disease when surgery first became available.

The need for valve replacement is obvious in patients with distinct symptoms or advanced congestive heart failure, but the decision is more difficult in the reasonably compensated patient with mild or moderate symptomatic limitations. To provide a uniform group of patients, only those with severe aortic regurgitation on a rheumatic basis were included. In this way, complications from additional factors such as medionecrosis of the aorta, syphilitic involvement of the coronary arteries, or important rheumatic involvement of other valves, were avoided.

In the Polynesian patients there is a high incidence of rheumatic heart disease and severe multivalve disease is common (New Zealand Department of Statistics, 1972). However, in the patient with 'isolated' aortic regurgitation, the clinical course is similar to that seen in the European counterpart.

Only 4 factors were associated with an increased incidence of preoperative deaths; heart failure, cardiomegaly (CTR >0·60), extreme left ventricular hypertrophy, and frequent ventricular premature beats. It is noteworthy that, though there was an association between symptomatic class and objective abnormalities (Table 3), clinical symptoms (shortness of breath, orthopnoea, paroxysmal nocturnal dyspnoea, or congestive heart failure were not more common in patients who died. In particular, there was no evidence that angina (unassociated with other unfavourable features) predisposed to premature death. Of the 4 objective factors, only a CTR more than 0·60 provided an indication for surgery when other factors were absent.

No preoperative factor was shown to predispose to unsatisfactory surgery. Postoperative deaths unrelated to technical problems or to bacterial endocarditis were too few to permit statistical conclusion. However, the only likely preoperative contributory factors were cardiomyopathy (usually because of undue delay in surgery despite advanced heart failure), considerable cardiomegaly (CTR>0·65) and, on occasion, advanced congestive heart failure at the time of operation or frequent ventricular premature beats. This conclusion awaits confirmation from a longer follow-up period but though the recorded follow-up period is short, further clinical reviews have shown no evidence of important change in patient status.

An attempt to define the natural history of severe aortic regurgitation has been made in previous publications. In the group of rheumatic cases described by Segal, Harvey, and Huffnagel (1956) the average age at the first attack of rheumatic fever was 13 years, and the average age at the development of haemodynamically significant aortic regurgitation was 20 years. An asymptomatic period of 10·3 years was followed by a symptomatic period of 6·4 years at the time of the study. In those patients affected, congestive heart failure was present for an average of 6·6 years and angina for 4·6 years. It should be noted, however, that, as in the present study, most of these patients were referred for surgical assessment and this may have excluded a number of patients who died prematurely. Even so, 5 per cent of the patients of Segal *et al.* (1956) died suddenly and unexpectedly. Similarly, Bland and Wheeler (1957) found that 37 per cent of their patients were able to lead relatively normal lives 10 years after the onset of aortic regurgitation and 26 per cent were well at 20 years. On the other hand, 38 per cent died within 10 years, and 56 per cent within 20 years.

The average time course of the disease will vary according to the method of selection of the group described. In the present study, a prolonged symptomatic period was relatively common, dyspnoea on exertion being noted for up to 20 years, symptoms of all three categories of heart failure for up to 10 years, and angina for up to 20 years. The prolonged survival of many patients with severe aortic regurgitation must be considered in deciding those features associated with a poor prognosis. DeGeorges and Delzant (1966) recorded a high death rate in patients who developed pulmonary oedema (9 out of 13 cases) or congestive heart failure (20 out of 24 cases). Massell, Amezcua, and Czoniczer (1966) reported the death of 13 out of 14 patients who developed congestive heart failure. Using a different approach Spagnuolo *et al.* (1971) defined the end point of the clinical course as the onset of angina, the onset of congestive heart failure, or death. They further defined a triad of (a) moderate or pronounced left ventricular hypertrophy radiologically, (b) two or three electrocardiographic abnormalities, and (c) an abnormal blood pressure with systolic pressure above 140 mmHg (18·6 kPa), or a diastolic pressure below 40 mmHg (5·3 kPa). We did not find the blood pressure significant in our group of patients, and we interpret Spagnuolo's results as indicating that an unfavourable outcome is related to the presence of severe left ventricular hypertrophy and important cardiac enlargement. This conclusion is in agreement with our own, but we believe measurement of CTR is preferable to a radiological attempt to assess left ventricular hypertrophy.

The onset of angina is usually considered a bad prognostic feature. Eight of the 9 patients with this symptom in the group described by Bland and Wheeler (1957) died within 2 years of onset and DeGeorges and Delzant (1966) reported average survival of 3 years in patients with angina. In these reports, the association of angina with other features received little attention. In the present series, all patients with angina who died without operation had additional unfavourable features, and the presence of preoperative angina did not affect early or late surgical results. Linhart *et al.* (1968) found significant coronary artery disease in 13 of 43 patients with aortic regurgitation, but the average age of these patients was 58 years. Coronary artery disease did not appear to be a significant feature in our patients. Angina was virtually always a function of advanced aortic regurgitation but it did not, in itself, constitute an indication for surgical intervention.

Braun, Kincaid, and McGoon (1973) have described a poorer early and late prognosis after surgery in patients with a preoperative CTR more than 0·57. We found no influence on postoperative outcome until the CTR was more than 0·65, though 'unexpected' preoperative death occurred in occasional patients with a CTR between 0·60 and 0·65.

It is possible that serial measurements of myocardial function might improve the assessment of the optimal timing of surgery, though interpretation of such measurements poses particular difficulties in patients with aortic regurgitation. Where repeated observations are required, non-invasive assessment has obvious merits and the simpler clinical observations used in this study have allowed a surprisingly accurate prediction of outcome. It remains to be seen whether this can be improved by the use of more sophisticated measurements.

The surgical risk for a young patient with aortic regurgitation is low and follow-up studies allow for increasing confidence in the long-term results of valve replacement. Even so, surgery is not warranted when it can be safely postponed. For the average patient with long-standing aortic regurgitation the surgical indications appear relatively clear cut.

1) Peripheral signs of a severe aortic valve leak. The natural history of aortic regurgitation of moderate severity is outside the scope of this paper, but in such patients surgery is required only in the presence of other complicating features.
2) A CTR of greater than 0·60. Other unfavourable features are usually present, but cardiomegaly of this magnitude is, in itself, usually an indication for surgery.
3) A history of heart failure (orthopnoea, paroxysmal nocturnal dyspnoea, or congestive heart failure) together with electrocardiographic evidence of extreme left ventricular hypertrophy, provides an indication for operation even if the CTR is less than 0·60.
4) Ventricular premature beats are unfavourable but are not an indication for surgery unless other major features are present.
5) Independent evidence of myocardial disease.

There is no evidence that any of the other factors studied should influence a decision for surgical intervention, for neither unexpected death nor a poor result after satisfactory surgery need be anticipated in the absence of the criteria outlined. Adherence to these criteria should, therefore, permit safe postponement of surgery in many cases. Admittedly, our patients constitute a selected group, but there is little published evidence of unexpected death in the absence of advanced disease. In the series of DeGeorges and Delzant (1966), death was preceded by signs of 'poor tolerance' in 30 out of 34 cases and the status of the other 4 patients was not known with certainty. A similar pattern is seen in the series of Spagnuolo *et al.* (1971). On the other hand, the mortality associated with the criteria described, suggests that surgery should not be delayed once these are fulfilled. Furthermore, the probable increase in surgical risk with emergency surgery on a patient *in extremis* and the unfavourable outcome after surgery in some patients with extreme cardiomegaly or advanced congestive heart failure preoperatively, are a clear enough indication that these situations should be avoided.

In the management of aortic regurgitation of non-rheumatic aetiology additional factors must be taken into consideration. Similarly, the situation is more complicated in the presence of important associated valvular anomalies.

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Effects of the cardioselective beta-adrenergic receptor blocking agent metoprolol in angina pectoris

Subacute study with exercise tests

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The effect of a cardioselective beta-adrenergic blocking agent, metoprolol[1]*, on symptoms and exercise tolerance was studied in 16 patients with angina pectoris.*

Metoprolol was compared with placebo at two dose levels (20 mg t.d.s. and 50 mg t.d.s.) in a double-blind trial in 14 patients. Compared with placebo, metoprolol caused a significant reduction of heart rate and systolic blood pressure during exercise, and consequently a reduction of the rate-pressure product. The reduction was greater with 50 mg t.d.s. than with 20 mg t.d.s. The exercise tolerance measured as total work increased significantly by 21 per cent during treatment with metoprolol 20 mg t.d.s., and by 17 per cent during treatment with 50 mg t.d.s. There was a reduction in the number of anginal attacks and in nitroglycerin consumption, and subjective improvement of angina pectoris at both dose levels of metoprolol. No signs of cardiac failure appeared during any of the four treatment periods. Heart volume showed no significant change. Unwanted effects were of the same frequency and severity during treatment with metoprolol at both dose levels as with placebo.

The sixteen patients were included in a long-term tolerance study with unchanged doses of metoprolol and have now been followed for 24 months without any unwanted effects.

In animal studies, metoprolol has been found to inhibit the heart rate and contractile force responses to isoprenaline in considerably lower doses than were required to block the vasodilator and bronchodilator effects of isoprenaline (Åblad, Carlsson, and Ek, 1973). By the criteria of Lands, Luduena, and Buzzo (1967), metoprolol selectively blocks beta$_1$-adrenergic receptors. Metoprolol has been found to be devoid of beta-receptor stimulating properties (Åblad *et al.*, 1973). Compared with placebo metoprolol significantly increased the exercise tolerance in patients with angina pectoris, in an acute study reported by Adolfsson *et al.* (1974). In view of these findings the present study was undertaken to evaluate the effects of metoprolol in patients with angina pectoris in a subacute study.

Subjects

Sixteen patients, previously treated with a beta-adrenergic blocking drug for angina pectoris for at least three months, entered the study. All had a typical history of angina pectoris by the criteria of Rose (1962). The mean age was 59 years (range 51 to 66 years), and the mean duration of angina pectoris was 6 years (range 6 months to 14 years). Nine patients had previously suffered myocardial infarction and four were treated with digoxin because of previous signs of heart failure. All patients but one had cardiac volumes within normal limits and one was at the upper limit of the normal range. Pertinent clinical information is given in Table 1.

Methods

During a run-in period of 3 weeks, the patients were treated with alprenolol 100 mg t.d.s. This was followed by a 3-week period of treatment with placebo and a 3-week period of treatment with metoprolol 20 mg t.d.s., and subsequently by 3-week periods of treatment with placebo and metoprolol 50 mg t.d.s. The sequence of treatment with metoprolol and placebo was randomized

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[1] Metroprolol is also known as H 93/26 (AB Hassle, Sweden) and CGP 2175 (Ciba-Geigy AG, Switzerland), and is marketed in the U.K. as Betaloc (Astra) and Lopresor (Geigy).

TABLE 1 *Clinical findings*

Case No.	*Sex*	*Age (yr)*	*Duration of angina pectoris (yr)*	*Supine heart volume (ml per m^2 BSA)*	*Previous myocardial infarction*	*Current treatment daily*
1	M	54	1	580	+	Digoxin 0 25 mg, antilipaemic drug
2	M	60	3	330	+	Clofibrate 2 g, nicotinic acid 3 g
3	M	66	11	450	+	Digoxin 0 25 mg, clofibrate 2 g
4	M	62	10	480	–	—
5	F	61	11	400	+	Clofibrate 2 g
6	F	64	7	420	+	Prednisolone 5 mg, mepacrine 5 mg, chlorthalidone 50 mg +KCl
7	M	59	4	440	+	Clofibrate 2 g
8	M	60	8	440	+	Digoxin 0·25 mg, anticoagulant
9	M	56	12	480	–	Chlorthalidone 50 mg+KCl, clofibrate 2 g
10	M	63	14	460	+	Dicoumarol
11	M	56	0·5	460	–	—
12	M	59	10	380	+	Chlorthalidone 100 mg+KCl, nicotinic acid 3 g
13	M	63	10	460	–	Nicotinic acid 3 g
14	M	51	2	No measurement	–	Nicotinic acid 3 g, dicoumarol
15	M	61	2	440	–	—
16	M	51	0·5	420	–	Digoxin 0·13 mg

at each dose level independently (Fig. 1). The metoprolol and placebo tablets used in this study were identical in size, shape, colour, and taste.

Patients were examined and had exercise tests at the end of each period. Laboratory tests were performed at the same times, as follows: haemoglobin, leucocyte count, platelets, ESR; serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, cholesterol, triglycerides, and uric acid; plasma sodium, potassium, and bicarbonate.

A. Clinical assessment

A simple diary card, to which the patients had become accustomed during the run-in period, was completed by the patient and returned to the physician at each visit. The diary card showed the number of nitroglycerin tablets taken each day, the number of anginal attacks, and a daily subjective assessment of angina pectoris according to a four-point scale. In addition, the patients were asked to express a general preference for each treatment period.

For statistical evaluation of the attack rate, the mean values for the 14 patients for each three-week period have been used.

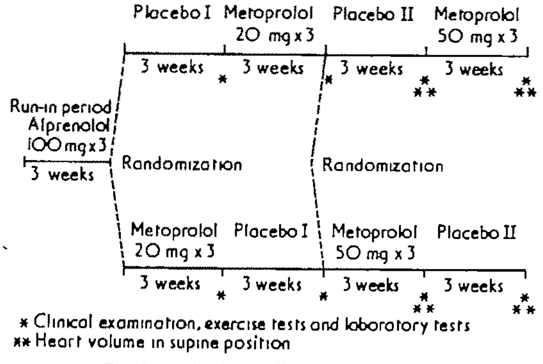

FIG. 1 *Design of the study.*

B. Exercise test

Exercise tests were performed in the sitting position on an electrically braked bicycle ergometer (Siemens-Elema EM 380) by a standardized procedure, with stepwise increasing work loads. The exercise tests were performed with six minutes at each work load; the increments of work load were so adjusted that the patients could complete at least two six-minute exercise periods before being stopped by chest pain during the third period. Electrocardiograms were monitored continuously and recorded intermittently during exercise using six praecordial leads (chest-head).

'Perceived exertion' was estimated on a 16-point scale (Borg, 1970). Corresponding scales were constructed for grading angina pectoris, dyspnoea, and the sensation of fatigue in the legs. Blood pressure was measured using the cuff method. Before exercise, systolic and diastolic pressures were recorded with the patient in the supine position and after 8 minutes standing. During exercise, systolic blood pressure was measured during the fifth minute at each work level. Cardiac volume was measured twice in the supine position (Kjellberg, Lönroth, and Rudhe, 1951).

Statistical significance was analysed by Student's t-test or Wilcoxon's matched pairs signed ranks test for comparison of paired data (Siegel, 1956; Snedecor and Cochran, 1967). The χ^2 test was used for evaluation of subjectively reported changes. All P values refer to two-tailed tests.

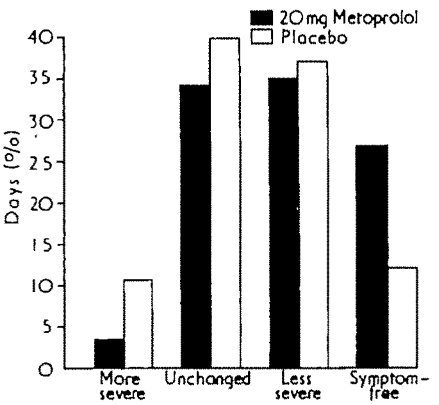

FIG. 2 *Daily subjective assessment of angina pectoris (metroprolol 20 mg t.d.s.). Statistical significance:* $\chi^2 = 9{\cdot}84$, $P = 0{\cdot}02$.

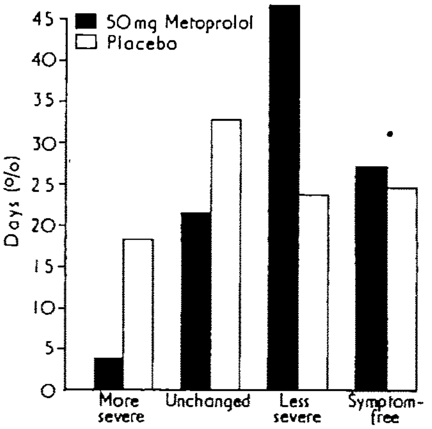

FIG. 3 *Daily subjective assessment of angina pectoris (metoprolol 50 mg t.d.s.). Statistical significance:* $\chi^2 = 19{\cdot}09$, $P < 0{\cdot}001$.

Results

Of 16 patients entering the study, 14 completed it. Cases 15 and 16 were excluded from the evaluation as they had less than five anginal attacks a week during placebo treatment. These two patients were on treatment with metoprolol for 12 months without any unwanted effects or abnormal results of laboratory tests.

A. Clinical assessment

The results are given in Table 2 and Fig. 2 and 3.

Attacks per week A significant reduction in the number of attacks compared with the corresponding placebo period was achieved with metoprolol 20 mg t.d.s. ($P < 0{\cdot}001$) but not with 50 mg t.d.s. However, it must be stressed that the two corresponding placebo periods were not identical. Cases 5, 8, and 12 had fewer anginal attacks during the second

TABLE 2 *Frequency of anginal attacks and nitroglycerin consumption*

Case	*Attacks per week*				*Nitroglycerin consumption (tablets/week)*			
No.	*Placebo* 20 mg	*Metoprolol* 20 mg	*Placebo* 50 mg	*Metoprolol* 50 mg	*Placebo* 20 mg	*Metoprolol* 20 mg	*Placebo* 50 mg	*Metoprolol* 50 mg
1	12	9	17	15	7	6	14	11
2	65[1]	23	–[2]	16	39[1]	15	–[1]	11
3	4	1	7	4	8	7	6	4
4	21	12	16	12	18	13	18	15
5	8	4	3	4	1	4	1	2
6	10	9	13	3	10	9	10	3
7	9	8	7	11	3	3	2	3
8	54	45	39	46	75	66	72	75
9	20	16	26	29	67	57	80	76
10	6	4	7	1	5	3	6	1
11	20	15	17	7	18	14	7	6
12	8	5	4	5	8	9	3	2
13	13	6	7[2]	3	5	2	4[2]	0
14	15	12	10	8	11	8	6	4
Median	12·5	9	10	7·5	9	8·5	6	4
Range	4–65	1–45	3–39	1–46	1–75	2–66	1–80	0–76
P	<0·001		NS		<0·05		<0·05	

[1] Angina worse, placebo discontinued after four days.
[2] Angina worse, placebo discontinued after two days.

TABLE 3 *Effect of metoprolol 20 mg and 50 mg on heart rate and blood pressure at rest and during exercise*

	Mean	*SEM*	*P*
Heart rate at rest, supine (beats/min)			
Metoprolol 20 mg (n=13)	62	2·0	<0·001
Placebo	74	2·8	
Metoprolol 50 mg (n=11)	58	2·3	<0·001
Placebo	74	2·0	
Heart rate at comparable work load (beats/min)			
Metoprolol 20 mg (n=12)	88	3·5	<0·01
Placebo	104	6·1	
Metoprolol 50 mg (n=11)	80	4·5	<0·001
Placebo	103	4·7	
Heart rate at end of work (beats/min)			
Metoprolol 20 mg (n=13)	96	4·6	<0·05
Placebo	115	6·1	
Metoprolol 50 mg (n=11)	90	4·9	<0·001
Placebo	119	6·3	
Blood pressure at rest; supine (mmHg)			
Metoprolol 20 mg (n=13)	133/81	4·9/2·6	<0·05/NS
Placebo	138/83	5·2/2·5	
Metoprolol 50 mg (n=11)	118/72	4·2/2·8	<0·001/<0·001
Placebo	137/85	5·0/2·4	
Systolic blood pressure at comparable work load (mmHg)			
Metoprolol 20 mg (n=12)	154	7·0	<0·05
Placebo	171	8·6	
Metoprolol 50 mg (n=11)	146	7·8	<0·01
Placebo	169	7·7	
Systolic blood pressure at end of work (mmHg)			
Metoprolol 20 mg (n=12)	159	7·9	<0·05
Placebo	180	8·2	
Metoprolol 50 mg (n=11)	160	7·9	<0·01
Placebo	187	10·0	
Rate-pressure product ($\times 10^{-2}$), at comparable work load			
Metoprolol 20 mg (n=12)	138	10·0	<0·01
Placebo	180	15·8	
Metoprolol 50 mg (n=11)	118	11·9	<0·001
Placebo	174	12·6	
Rate-pressure product ($\times 10^{-2}$) at end of work			
Metoprolol 20 mg (n=12)	157	13·6	<0·05
Placebo	207	18·7	
Metoprolol 50 mg (n=11)	146	13·1	<0·001
Placebo	222	20·0	

Conversion factor from Traditional Units to SI Units: 1 mmHg ≈ 0·133 kPa.

placebo period than during the period on treatment with metoprolol 50 mg t.d.s.

Nitroglycerin consumption was significantly reduced by metoprolol at both dosage levels, compared with the corresponding placebo periods (P <0·05) (Table 2).

A significant improvement was also apparent from the patients' *subjective daily assessment* of their angina, both with metoprolol 20 mg t.d.s.

(P < 0·02) (Fig. 2) and with the dosage of 50 mg t.d.s. (P < 0·001) (Fig. 3).

The *general preference* at the end of each period showed that 8 patients had a clear preference for metoprolol 20 mg t.d.s. compared with placebo, and 10 patients for metoprolol 50 mg t.d.s. compared with placebo.

B. Cardiovascular effects at rest and during exercise (Tables 3 and 4).

Case 4 was excluded from this evaluation because he was unable to exercise on the bicycle. Two patients (Cases 2 and 13) did not tolerate placebo treatment, because of worsening of their angina, and were switched over to active drug treatment after a few days. Neither of these patients was able to exercise during the second placebo period.

Mean values for heart rate, blood pressure, and rate-pressure product during exercise are given in in Table 3.

Heart rate Calculations of the mean values showed that metoprolol at both dose levels produced a significant reduction in resting heart rate, heart rate recorded at comparable work load, and heart rate at the end of exercise, compared with placebo. The effect was greater at the higher dose.

Systolic blood pressure measured resting supine, at comparable work load, and at the end of exercise, was also significantly reduced with both doses.

Rate-pressure product was significantly reduced with both doses of metoprolol at comparable work load, and at the end of exercise. The reduction was greater with the dosage of 50 mg t.d.s.

Total work was calculated as the product of work load in Watts and number of minutes of exercise. There was a statistically significant increase in total work with metoprolol at both 20 mg t.d.s. (P < 0·05), and 50 mg t.d.s. (P < 0·05), compared with placebo (Table 4).

Work load at break point, the highest calculated load tolerated for 6 minutes (Ekelund, Melcher, and Orö, 1974), increased significantly with metoprolol 20 mg t.d.s. (P < 0·05) and 50 mg t.d.s. (P < 0·01) compared with placebo.

Eight patients increased their total work by 20 per cent or more on the dosage of 20 mg t.d.s. compared with placebo. These patients are regarded as responders to the dosage of 20 mg t.d.s. Three patients increased their total work by more than 20 per cent on the dosage of 50 mg t.d.s. Two patients (Cases 2 and 13) did not perform any exercise test during the second placebo period because of worsening of angina pectoris, and were switched over to metoprolol 50 mg t.d.s. after a few days. These 5 patients are regarded as responders to the dosage of 50 mg t.d.s. Cases 6, 12, and 14 are regarded as responders to the 20 mg t.d.s. but not to 50 mg t.d.s. However, these 3 patients showed a distinct improvement in exercise tolerance when the second placebo period was compared with the first.

The *perceived exertion, angina pectoris, dyspnoea,* and sensation of *fatigue in the legs* were not significantly affected, by either dose of metoprolol.

Cardiac volume, calculated as total volume, showed no significant differences at the end of the treatment periods with metoprolol 50 mg t.d.s. or placebo.

Complications and unwanted effects

Two patients (Cases 2 and 13) did not tolerate the placebo because of worsening of angina pectoris, and were, therefore, given active drug treatment after 2 to 4 days. One patient (Case 4) complained of dizziness on metoprolol 50 mg t.d.s., but when the dose was halved, this symptom disappeared. The frequency of unwanted effects was low and about the same during treatment with metoprolol and placebo.

All 16 patients were included in a long-term tolerance study with unchanged doses of meto-

TABLE 4 *Effect of metoprolol on total work and work load at break point*

	Metoprolol (20 mg t.d.s.)	*Placebo*	*% change from placebo*	*Metoprolol (50 mg t.d.s.)*	*Placebo*	*% change from placebo*
Total work (W min) (n=13)						
Mean	596	492	21	672	581	17
SEM	87·4	84·0		79·3	89·6	
Range	110–1080	120–1080		300–1080	143–1080	
P	<0·05			<0·05		
Work load at break point (W) (n=13)						
Mean	56·4	49·4	14	60·7	55·9	9
SEM	6·49	6·66		5·77	6·43	
Range	18·3–90·0	15·4–90·0		30·90	21·3–90·0	
P	<0·05			<0·01		

prolol. Thus, one patient had 25 mg t.d.s. and the remainder had 50 mg t.d.s. Patients were examined after 6, 12, 18, and 24 months' treatment with metoprolol. The following laboratory investigations were done: haemoglobin, white blood cell count, and ESR; serum creatinine, bilirubin, alkaline phosphatase, AST, ALT, cholesterol, triglycerides, uric acid, and antinuclear factor (ANF).

During the long-term tolerance study, one patient had a non-fatal myocardial infarction. In the whole group no severe unwanted effects were observed and there were no abnormal laboratory findings. Blood pressure and body weight remained unchanged throughout the study.

Discussion

This study was performed to evaluate the anti-anginal effect of metoprolol in 16 patients previously treated with alprenolol. As this was one of the first studies with chronic metoprolol treatment in angina pectoris, the study was designed to evaluate response to two dosage levels, with 20 mg t.d.s. always preceding 50 mg t.d.s.

The results of the exercise test show that total work was significantly increased, compared with placebo, by about 20 per cent after both dose levels of metoprolol. The increase in exercise tolerance was largest in the patients who had a decrease or only a very small increase in cardiac volume after metoprolol. Determination of the cardiac volume in combination with exercise tests might thus be of value for evaluating the effect of a beta-receptor blocking agent (Jonsson, Olsson, and Orö, 1973). The increase in exercise tolerance was of the same magnitude as reported by Adolfsson *et al.* (1974) and was accompanied by a corresponding subjective improvement. The reduction of heart rate and systolic blood pressure was of the same magnitude as in the acute study by Adolfsson *et al.* (1974).

All the patients were well known to us, having been treated for long periods, were familiar with exercise testing, and could be regarded as having stable angina pectoris. Therefore, only minor differences were expected to appear between the two placebo periods. However, many of the patients showed unexpected improvement during the second placebo period, with both reduction in frequency of angina and increased exercise capacity. This difference in exercise tolerance between placebo periods could be attributed to increased activity and physical fitness resulting from previous treatment. The effect of the exercise testing on exercise capacity could certainly be neglected. This improvement during the second placebo period probably had an unfavourable effect on the apparent results of treatment with 50 mg t.d.s. relative to treatment with 20 mg t.d.s. of metoprolol. Therefore, from the results of the present investigation it is difficult to state which of the two dosage levels used is the optimal one.

However, if only the median and mean values are taken into consideration, there was an improvement during the 50 mg t.d.s. treatment period compared with the 20 mg t.d.s. period. These results suggest that 20 mg t.d.s. is a suitable initial dose of metoprolol, and that many patients derive further benefit from 50 mg t.d.s. In this study, neither of the doses used induced any clinically significant unwanted effects nor were there any abnormal findings in the laboratory tests.

Both the increase in exercise tolerance and the subjective improvement indicate that metoprolol is effective in angina as are other beta-adrenergic blocking agents (Dagenais, Pitt, and Ross, 1971; Adolfsson, Areskog, and Rasmuson, 1971; Hetherington *et al.*, 1973). Furthermore, metoprolol should have advantages resulting from its selective effect on beta$_1$-adrenergic receptors, especially in patients with bronchial asthma, and could in special cases be combined with a beta$_2$-stimulating agent such as salbutamol or terbutalin (Thiringer and Svedmyr, 1976).

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Cardiomyopathy complicated by left ventricular aneurysms in children

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Ventricular aneurysms in children are unusual. Three patients with cardiomyopathy associated with angiographically proved left ventricular aneurysms in this age group are reported. Two of them were girls. The ages were 20 months, 7 years, and 14 years. Heart failure was present in all patients. There was radiological evidence of cardiomegaly in all three, and the electrocardiogram showed signs of necrosis in two of them. Selective left ventricular angiography disclosed generalized hypokinesis in all patients. One child had an aneurysm of the diaphragmatic wall. In another the aneurysm was localized in the muscular ventricular septum, causing severe subpulmonary stenosis by encroaching in the right ventricular outflow tract during systole. The third patient had an aneurysm of the left ventricular free wall partly encircling the left ventricle. The coronary arteries appeared normal in all cases. The clinical features of the underlying disease were not altered by the presence of the aneurysm except in the patient with the septal aneurysm and subpulmonary stenosis. In this patient the aneurysm was successfully resected.

The commonest cause of left ventricular aneurysm in adults is ischaemic heart disease (Cheng, 1971). Unusual causes for this lesion include syphilis (Braunstein, Bass, and Thomas, 1940), tuberculous granuloma (Beheyt and VandenPutte, 1958), mycotic embolism (Layman and January, 1967), Chagas's disease (Moia, Rosenbaum, and Hojmen, 1955), fungal endocarditis (Mershon, Samuelson, and Layman, 1968), nonspecific myocarditis (Moreyra *et al.*, 1972), and cardiac sarcoidosis (Lull *et al.*, 1972). They may also be secondary to chest trauma (Killen *et al.*, 1969), or surgery (Wychulis *et al.*, 1971).

Left ventricular aneurysms in children are extremely unusual. They may be congenital (Paronetto and Strauss, 1963; Ruttenberg *et al.*, 1964; Treistman *et al.*, 1973), secondary to anomalous origin of the left coronary artery from the pulmonary trunk (Bland, White, and Garland, 1933), or result from rubella myocarditis (Van der Horst and Gotsman, 1970). Calcific apical aneurysms occurring almost exclusively in Africans (Pocock *et al.*, 1965) have also been described in this age group.

It is the purpose of this communication to present three children with cardiomyopathies and angiographically proven left ventricular aneurysms.

Case reports

Case 1

A 14-year-old mentally retarded girl with no relevant past and family history was admitted to the hospital in severe congestive heart failure. She was put on bed rest, given diuretics and digitalis, but showed obvious intolerance to the latter, experiencing frequent arrhythmias. She had cardiomegaly and gallop rhythm. There were no murmurs. Laboratory studies were normal. A chest *x*-ray obtained at the time of the cardiac catheterization disclosed an enlarged heart with a cardiothoracic ratio of 0·54. The aortic knuckle was small and the pulmonary vasculature appeared normal. The electrocardiogram showed sinus rhythm alternating with episodes of atrial fibrillation. There was left atrial enlargement, left axis deviation (ÂQRS −30°), and diffuse ST-T abnormalities. Bradycardia, sinus arrests, second degree atrioventricular block, and frequent ventricular extrasystoles were seen while the girl was under treatment with digitalis.

A combined cardiac catheterization showed normal

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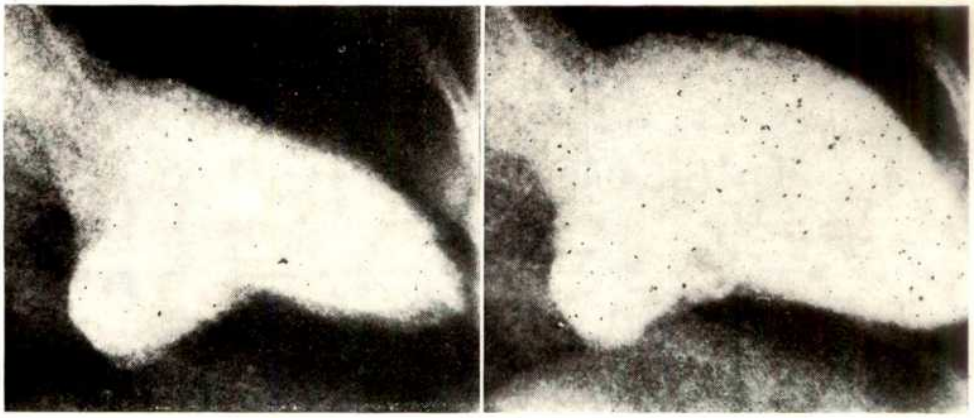

(a) (b)

FIG. 1 *Left ventricular cineangiography in the right anterior oblique projection, (a) in systole and (b) in diastole in Case 1. There is mitral regurgitation and a moderate-size aneurysm of the diaphragmatic wall.*

intracardiac pressures except for the right ventricular end-diastolic and the right atrial mean pressures, which were raised (Table). The cardiac index was low at 2·4 l per min per m² b.s.a. Selective left ventricular cineangiocardiography in the right anterior oblique projection disclosed extensive impairment of the left ventricular contractility, with an ejection fraction of 49 per cent. A medium size subvalvular aneurysm was present in the diaphragmatic wall as well as grade 2 mitral regurgitation (Fig. 1). The aorta and coronary arteries appeared normal in the retrograde aortogram.

The patient was discharged with the diagnosis of cardiomyopathy and maintained on medical treatment. Three months later she was readmitted in severe congestive heart failure unresponsive to treatment, dying shortly after. Necropsy was not permitted.

Case 2

A 20-month-old boy presented at the age of 20 days in congestive heart failure. The diagnosis of congenital heart disease was made, and thereafter he was maintained on digoxin, with a good clinical response. On physical examination he was well developed for his age. There was clinical evidence of cardiomegaly. Auscultation of the heart revealed a 4/6 ejection systolic murmur best heard along the left sternal border. There was a loud ejection sound present only on inspiration. The second heart sound was normally split, with a soft and delayed pulmonary component. Laboratory studies were normal. The chest *x*-ray showed cardiomegaly with a cardiothoracic ratio of 0·60. The apex of the heart was uptilted, and the pulmonary vasculature was within normal limits. The electrocardiogram (Fig. 2) had an ÂQRS axis of +15° in the frontal plane. The QRS width was 0·10 s. There were deep Q waves from V1 to V4. Tall and slurred R waves were present in the right praecordial leads. Leads V5 and V6 showed increased voltage of the R waves and slurred S waves. In summary, the tracing was compatible with incomplete right bundle-branch block, biventricular hypertrophy, and anteroseptal wall necrosis.

A combined cardiac catheterization was performed showing a 57 mmHg (7·6 kPa) gradient between the right ventricular inflow and outflow tracts (Table). The systolic pressure of the right ventricular sinus was close to systemic level. The cardiac index was normal at 5·3 l per min per m² b.s.a. No shunts were demonstrated by oximetry or cineangiography. Right ventricular cineangiography in the lateral view showed a round filling defect in this cavity encroaching on the outflow tract. The return circulation to the left heart showed filling of a large septal aneurysm of the left ventricle which corresponded to the filling defect visualized in the right ventricle (Fig. 3). The left ventricular cineangiogram in the right anterior oblique projection showed poor contractility (35% ejection fraction). A retrograde aortogram disclosed normal coronary arteries.

Two years after the initial study the child was re-examined. He complained of moderate fatigue and dyspnoea on effort. The auscultatory findings, electrocardiogram, and chest *x*-rays were essentially unchanged. A repeat cardiac catheterization showed a more severe obstruction to right ventricular outflow (80 mmHg (10·6 kPa) gradient) (Table). Left ventriculograms in both oblique projections showed again impaired left ventricular contractility (40% ejection fraction), and a large multiloculated aneurysm of the ventricular septum impinging in the right ventricular outflow tract.

Open heart surgery was performed shortly after the second haemodynamic study. The right ventricular cavity was partially occupied by a fibrous saccular aneurysm arising from the muscular septum which was 4 cm long and 2 cm wide. A membranous ventricular septal defect measuring 7 mm in diameter and hidden by the aneurysm was found. The defect was infracristal and was separated by 15 mm from the base of implanta-

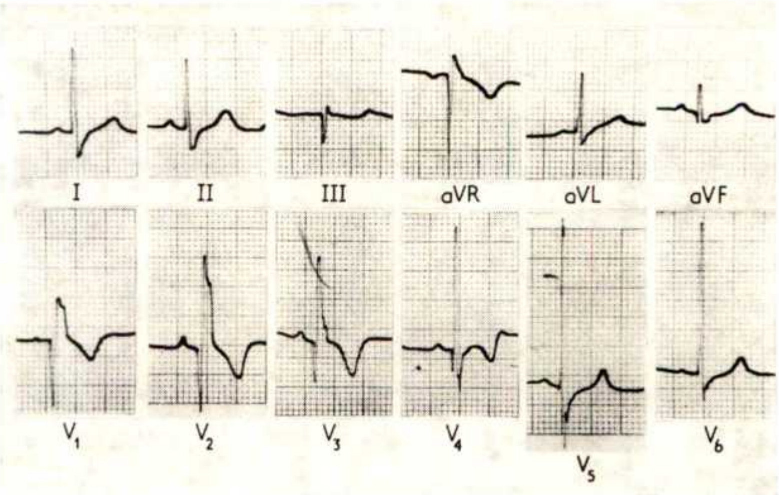

FIG. 2 *Electrocardiogram of Case 2. There is evidence of left ventricular hypertrophy, incomplete right bundle branch block, and anteroseptal wall necrosis.*

tion of the aneurysm. The aneurysm was resected and the ventricular septal defect was closed with separate stitches. The patient made an uneventful recovery.

Pathological findings

The aneurysm was whitish in colour and dome shaped. The maximal length was 4 cm, and the thickness varied between 2 and 3 mm. The surface was smooth on the convex side and slightly rugose on the opposite side. Microscopy showed that the muscular cardiac fibres were replaced by thick fibrous tissue with zones of hyalinization. There were scattered islets of myocardial fibres surrounded by the fibrous tissue. Inflammatory cells were not found.

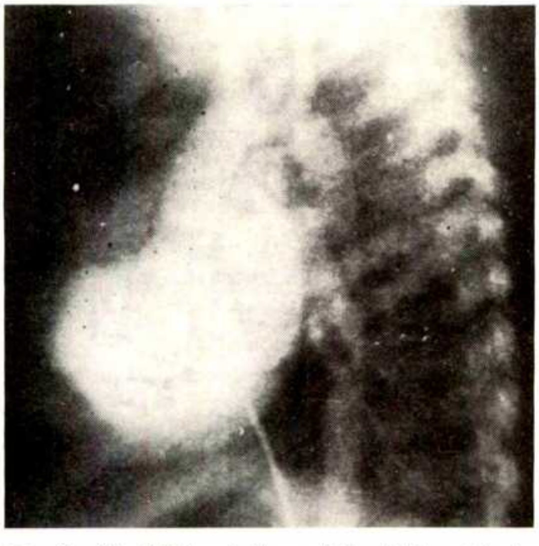

FIG. 3 *The left heart-phase of the right ventricular angiocardiogram in the lateral projection of Case 2 showing a large, multiloculated aneurysm of the ventricular septum.*

Case 3

A 7-year-old well-developed girl with no relevant past and family history was asymptomatic up to the age of 6 years, when dyspnoea and fatigue were noted. Physical examination disclosed a heart murmur, and she was referred for investigation. There was clinical evidence of cardiac enlargement. The first heart sound was soft, and the second sound was slightly accentuated and normally split. A 2/6 ejection systolic murmur was heard along the left sternal border. Chest *x*-rays showed an enlarged heart with a cardiothoracic ratio of 0·56 and normal pulmonary vasculature. The electrocardiogram showed left ventricular hypertrophy and primary T wave abnormalities. There were abnormal Q waves in leads II, III, and aVF.

Cardiac catheterization showed normal pressures in both sides of the heart and no shunts (Table). The cardiac index was 4·8 l per min per m^2 b.s.a., and the maximal dP/dt was moderately decreased to 1260 mmHg/s (167·6 kPa/s). Selective left ventriculography in both oblique projections showed an enlarged left ventricle with diffuse hypokinesis and delayed emptying. A large, bilobed, crescent-shaped aneurysm arising from the left ventricular free wall, surrounded most of the ventricle (Fig. 4).

She was discharged on digitalis and six months later was restudied. The heart size had increased, and there were frequent ventricular premature beats. Left heart

TABLE *Haemodynamic data*

	Pressures (mmHg)							
	Case 1 *14 yr*		*Case 2* *1 yr 8 mth*		*3 yr 8 mth*		*Case 3* *7 yr*	
Right atrium		(10)		(4)		(3)		(3)
Right ventricle								
inflow	28/10		85/6		110/6		22/8	
outflow			28/6		30/6			
Pulmonary artery	28/13	(20)	26/8	(15)	28/10	(15)	22/12	
P A wedge		(11)	—			(5)		(9)
Pulmonary vein	—			(10)		(5)	—	
Left atrium	—			(8)		(5)	—	
Left ventricle	110/11		96/8		110/9		110/7	
Aorta	100/80	(86)	98/68	(80)	105/60	(75)	110/65	
Cardiac index (l/min per m^2)	2·37		5·35		4·91		4·8	
Ejection fraction	49%		35%		40%		—	

Numbers in brackets represent mean pressures. Left atrial and pulmonary vein pressures in Case 2 were obtained through a patent foramen ovale. Conversion factor from Traditional to SI units. 1 mmHg≈0·133 kPa.

catheterization disclosed further decrease of the maximal dP/dt to 700 mmHg/s (93·1 kPa). The coronary arteries were selectively opacified and appeared completely normal.

Discussion

Left ventricular aneurysms are very frequent in adults owing to the high incidence of ischaemic heart disease. Other causes are rare. On the other hand, the occurrence of left ventricular aneurysms in children is extremely unusual.

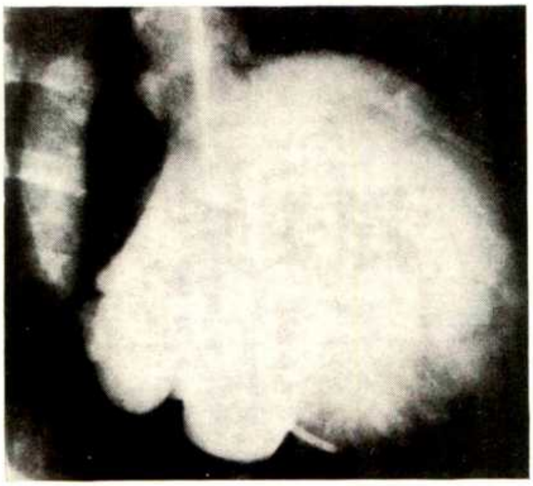

FIG. 4 *Left ventriculography in the right anterior oblique projection of Case 3. A crescent-shaped bilobed aneurysm encircling the ventricle is clearly seen. The left ventricular cavity is huge.*

Our first patient had the clinical features of a congestive cardiomyopathy. The obvious cardiomegaly with diffuse impairment of the left ventricular contractility favours the generalized involvement of the myocardium. The location of the aneurysm in the diaphragmatic wall indicates that this was the area of maximal weakness. We have recently seen three adults with similar aneurysms in the presence of normal coronary arteriograms (Moreyra *et al.*, 1972).

The second patient of our series is unique because the aneurysm involving the muscular ventricular septum produced severe subpulmonary stenosis. The paradoxical movement of the aneurysm during systole made it protrude into the right ventricular outflow tract. This type of obstruction to right ventricular outflow is similar to that found in some cases of aneurysms of the membranous ventricular septum (Das, Jahnke, and Walker, 1964), which often accompany small ventricular defects. In our patient there was also a membranous defect which had not been evident until surgery despite two haemodynamic studies and selective left ventricular cineangiograms previously performed. It appears that the defect was occluded by the redundant aneurysmal sac arising from the muscular septum.

This child's electrocardiogram showed anteroseptal wall necrosis. Coronary arterial anomalies were ruled out by retrograde aortography. A case of myocarditis caused by neonatal rubella showing an infarct pattern in the electrocardiogram and complicated by a left ventricular aneurysm has been reported by Van der Horst and Gotsman (1970). Our patient had no rubella stigmata but other intrauterine viral infection cannot be excluded. A myocardial infarct with normal coronary arteries, which is being recognized with increasing frequency in young adults (Khan and Haywood, 1974), is another possibility, though unlikely. Histological studies of the resected aneurysm showed that this was a fibrous structure with scattered myocardial fibres. Inflammatory cells were not present. However, since more than three years had elapsed from birth a myocarditis causing the original lesion could not be ruled out.

The last patient of our series also had evidence of myocardial disease with impaired left ventricular function. The electrocardiogram showed inferior wall necrosis and left ventricular hypertrophy. In this case the aneurysm had a very unusual crescent shape surrounding most of the left ventricular cavity. The coronary arteries were normal. To the best of our knowledge there are only two apparently similar cases reported. Paronetto and Strauss (1963) and Ruttenberg *et al.* (1964) found loculations and septations within the left ventricle corresponding to areas of myocardial wall hypoplasia and bridges formed by hypertrophied myocardial fibres. Their cases were probably congenital in origin, as we think is ours.

The three patients of this series are examples of cardiomyopathy of unknown origin complicated by left ventricular aneurysms. The presence of areas of localized weakness of the affected myocardium is the possible mechanism for aneurysm formation. The clinical features of the cardiomyopathy were not altered by the presence of the aneurysm except in the patient with subpulmonary stenosis caused by the aneurysm of the ventricular septum. In this child surgical resection of the aneurysm was carried out successfully.

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Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy

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Twelve patients with congestive heart failure receiving maintenance therapy with digoxin and potent diuretics were followed closely during development of hypokalaemia and potassium loss. Cardiac arrhythmias compatible with digoxin toxicity developed in 6 patients in the presence of stable, normal serum digoxin concentrations. The mechanisms involved in the development of the rhythm disturbances are discussed with regard to hypokalaemia, intracellular potassium loss, intra-/extracellular potassium gradients and digoxin, and the significance of maintaining a normal potassium balance in this setting is stressed.

It is generally accepted that hypokalaemia and potassium loss may promote digitalis toxicity in patients with congestive heart failure receiving maintenance treatment with digitalis. However, while this situation was frequent in earlier studies of digitalis toxicity (Lown and Levine, 1954; Jorgensen and Sorensen, 1970), hypokalaemia and potassium loss were not observed as causes of digitalis intoxication in more recent reports (Beller *et al.*, 1971; Evered and Chapman, 1971). Though this new trend may reflect better treatment with regard to maintenance of potassium balance during digitalis therapy in particular in patients on chronic diuretic therapy, it seems also possible that the risks involved in hypokalaemia and potassium loss in this setting have been overestimated in the past. In earlier studies of digitalis toxicity in man the relative role of digitalis overdosage and of acute or chronic hypokalaemia or potassium loss have not been precisely defined, and more recent studies in dogs have not supported the concept that hypokalaemia sensitizes the myocardium to digitalis during conditions representing the nearest practical approximation to the situation of patients on chronic diuretic therapy (Kleiger, Vitale, and Lown, 1965; Binnion, 1975).

In an attempt to clarify the significance of hypokalaemia and total potassium deficiency and to evaluate the role of serum digoxin levels in this setting, the present study was planned. Twelve patients with advanced heart failure receiving maintenance therapy with digoxin and potent diuretics were subjected to a potassium depleting regimen and followed closely for development of cardiac arrhythmias while serum digoxin concentrations were controlled.

Methods

Twelve patients with advanced congestive heart failure admitted to Medical Department B, Rigshospitalet Copenhagen, were selected for study according to the following criteria: 1) The subjects had received maintenance digoxin therapy for at least one month and showed normal serum digoxin levels, 2) the patients were in a stable situation on maintenance diuretic treatment, and 3) the subjects presented normal serum potassium concentrations and were apparently in a stable potassium balance while receiving a standard supplement of potassium chloride of 3 g daily or a potassium sparing drug as additional diuretic if required. The series consisted of 5 men and 7 women; mean age 57·7 years. The clinical diagnoses were rheumatic valvular disease in 6 patients, ischaemic heart disease in 4, and cardiomyopathy in 2. The patients received maintenance treatment with digoxin in a dose range from 0·125 to 0·50 mg daily and frusemide 80 to 160 mg or bumetanide 4 to 6 mg per day.

With their informed consent the patients were studied according to the following plan: the electrocardiogram was monitored continuously permitting rapid discontinuation of the study and restoration of potassium balance if required. The maintenance therapy with digoxin and potent diuretics was continued while potassium chloride and potassium sparing drugs were withheld. The patients were studied on a metabolic regimen including a diet restricted in potassium (30 mEq daily). Twenty-four hour urinary volumes and excretion of

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potassium were measured. Body weight was determined every morning. At the start of the study total exchangeable potassium (K_e) was measured by dilution with K^{42} (Olesen, 1964). Serum potassium and creatinine were determined every morning (normal range for serum K: 3·5–5·1 mmol/l). Serum digoxin was measured in the fasting state at the start and the end of the study (Steiness, 1974). The study was planned to last 7 days for each patient, but was interrupted immediately if significant arrhythmias occurred.

Serum thyroxine was measured in 10 patients and found to be within the normal range.

Calculation of potassium balance

The cumulative balance of potassium was determined as summations of daily intakes—renal outputs corrected for faecal and insensible losses (Isaksson, Lindholm, and Sjogren, 1966; Maronde, Milgrom, and Dickey, 1969). The cumulative negative potassium balance was partitioned into extra- and intracellular losses, and the intra-/extracellular potassium gradients were derived as follows.

a) Abbreviations ECW = total extracellular water, (K)s = serum potassium concentration, ECK = total extracellular potassium, ICK = total intracellular potassium, K_e = total exchangeable potassium (assumed to represent initial body potassium), K_{io} = intracellular potassium concentration, ICW = total intra-cellular water, '1→n' indicates the cumulative 24-hour periods of investigation.

b) Starting values ECW_0 = body weight$_0$ × 0·3, $ECK_0 = ECW_0 \times (K)s_0$, $ICK_0 = K_e - ECK_0$, $ICW_0 = ICK_0/160$, gradient$_0$ = $K_{io0}/(K)s_0$. The basic assumption was made that the average intracellular K concentration of the body and of the myocardium was 160 mmol/l. at the start of the study (Valentin and Olesen, 1973).

c) Cumulative balance values $ECK_{1\to n} = (ECW_0 -$ weight loss$_{1\to n}) \times (K)s_{1\to n}$, $\Delta ECK_{1\to n} = ECK_{1\to n}$, ECK_0, $ICK_{1\to n} = ICK_0 + (\Delta K$ balance$_{1\to n} - \Delta ECK_{1\to n})$, $\Delta ICK_{1\to n} = ICK_{1\to n} - ICK_0$, $K_{ic1\to n} = ICK_{1\to n}/ICW_0$.

Intra-/extracellular potassium gradients were calculated according to two models. *Model I:* gradient $I_{1\to n} = K_{io1\to n}/(K)s_{1\to n}$, Δgradient $I_{1\to n}$ = gradient $I_{1\to n}$ — gradient I_0. *Model II:* gradient II was calculated as shown above under the assumption that the myocardial intracellular potassium concentration remained unchanged during the study (Bolte, 1973).

Interpretation of electrocardiogram

The continuous monitoring of the electrocardiogram and tracings of one minute's duration taken at least twice daily were analysed for arrhythmias, usually ascribed to digoxin toxicity (Evered and Chapman, 1971).

Results

Cardiac arrhythmias occurred in 6 out of 12 patients (50%) within the week of the study. Four patients developed ventricular premature beats either as multifocal ectopic beats or as bigeminy. Two patients showed atrial premature beats with prolonged PQ intervals. All 6 patients showed hypokalaemia and overall potassium loss when the arrhythmias occurred. In 2 patients interruption of the study became necessary after 3 and 4 days because of the development of rhythm disturbances. In the remaining 4 patients the arrhythmias only occurred on the last day of the study.

Serum digoxin concentrations showed a mean value of 1·52 ± 0·17 nmol/ml (1·19 ± 0·13 ng/ml) at the start of the study and did not change significantly during the experiment. The daily oral dose of digoxin was 0·30 ± 0·06 mg. As shown in Table 1 the mean values and the trends were exactly the same in the group developing arrhythmias and in the group without. Similarly, serum creatinine concentrations were the same in the two groups and remained unchanged during the study.

TABLE 1 *Summary of data in patients on maintenance digoxin therapy (mean values ± SEM)*

	No.	*Age (yr)*	*Average daily digoxin dose (mg)*	*Serum digoxin concentration (nmol/ml)*		*Serum creatinine concentration (mmol/l)*	
				Before	*After*	*Before*	*After*
All subjects	12 M:5, F:7	57·7 ±3·7	0·30 ±0·06	1·52 ±0·17	1·69 ±0·23	0·11 ±0·01	0·11 ±0·01
Subjects developing arrhythmias	6 M:2, F:4	59·5 ±3·9	0·28 ±0·04	1·51 ±0·29	1·63 ±0·37	0·11 ±0·01	0·11 ±0·01
Subjects not developing arrhythmias	6 M:3, F:3	55·8 ±6·6	0·32 ±0·05	1·54 ±0·18	1·77 ±0·23	0·11 ±0·02	0·11 ±0·01

Conversion from SI to traditional units: digoxin 1 nmol≈0·78 ng.

TABLE 2 *Summary of data on potassium balance (absolute values given as mean values ± SEM)*

	No.	*Serum potassium (mmol/l) Before*	*After*	*Total exchangeable potassium (mmol)*	*Total K balance (mmol)*	*Total extracellular K balance (mmol)*	*Total intracellular K balance (mmol)*
All subjects	12	4·37 ±0·10	3·41 ±0·09	1890 ±125	−204 ±18	−21 ±2	−183 ±20
Subjects developing arrhythmias	6	4·45 ±0·13	3·45 ±0·15	1918 ±241	−204 ±26	−24 ±3	−180 ±27
Subjects not developing arrhythmias	6	4·28 ±0·17	3·37 ±0·13	1861 ±106	−204 ±32	−18 ±4	−184 ±31

Potassium metabolism

As shown in Table 2 the regimen used proved effective in reducing serum potassium concentration from a mean value of 4·37 mmol/l at the start to a mean of 3·41 mmol/l at the end of the study. The development of hypokalaemia was associated with a mean total potassium loss of 204 mmol. 21 mmol (or 10% of total potassium loss) originated from the extracellular phase while the remaining 183 mmol (or 90% of total potassium loss) was lost from the intracellular phase. The cumulative changes in potassium balance for 10 patients studied for a full week is shown in Fig. 1. Apparently, the decrease of serum potassium concentration and of total body potassium was most pronounced during the first 4 to 5 days of the study.

The degree of hypokalaemia and of total potassium loss obtained was very similar in the group developing arrhythmias to that in the group without (Table 2).

For the whole group the total potassium loss amounted to 11 per cent of initial body potassium (Table 3). Of particular significance is the fact that the total extracellular loss represents 26 per cent of the initial total extracellular potassium whereas the total intracellular loss amounts to only 11 per cent of the initial total intracellular potassium. The relatively larger loss from the extracellular phase results in a rise in the intra-/extracellular potassium gradient 1 (model I) for the whole body (Table 3 and Fig. 2). An even larger rise is seen in the myo-

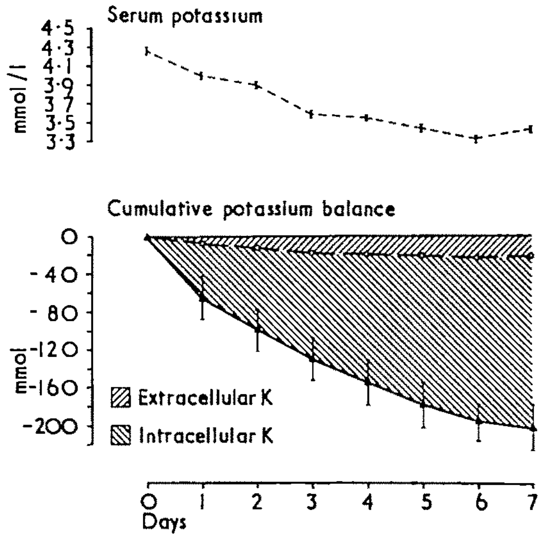

FIG. 1 *Serum potassium concentration and cumulative K balance in* 10 *patients receiving a K depleting regimen for* 7 *days. Mean values (±SEM) are given.*

TABLE 3 *Summary of data on potassium balance (relative values given as mean values ± SEM)*

	No.	*Total K loss as % of initial body K (%)*	*Total extracellular K loss as % of initial total extracellular K (%)*	*Total intracellular K loss as % of initial total intracellular K (%)*	*Change of intra-/extracellular K gradient I*	*Change of intra-/extracellular K gradient II*
All subjects	12	−11·3 ±1·3	−26·1 ±2·1	−10·7 ±1·4	+4·2 ±1·8	+9·6 ±1·6
Subjects developing arrhythmias	6	−11·7 ±2·5	−28·1 ±1·7	−11·1 ±2·6	+4·6 ±1·7	+10 7 ±1·3
Subjects not developing arrhythmias	6	−10·8 ±1·3	−24·0 ±3·9	−10·3 ±1·3	+3·8 ±3·3	+8·5 ±3·2

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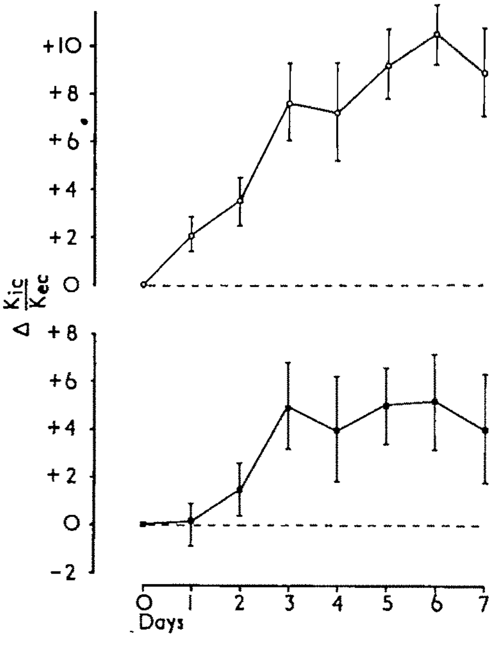

FIG. 2 *Changes in intra-/extracellular K gradients in* 10 *patients receiving a K depleting regimen for* 7 *days. Mean values* (±*SEM*) *are given. The upper panel shows the myocardial K gradient (calculated on the assumption of an unchanged intracellular K concentration); the lower panel shows the K gradient for the whole body.*

cardial intra-/extracellular potassium gradient II (model II) which is derived on the assumption that myocardial intracellular potassium concentration remains unchanged while distinct hypokalaemia develops (Table 3 and Fig. 2).

The partitioning of the potassium loss and the changes in intra-/extracellular potassium gradients were the same in the group developing arrhythmias and in the group without (Table 3).

Discussion

The study was performed in patients with advanced congestive heart failure receiving maintenance digoxin therapy. The mean serum digoxin concentration was 1·52 ± 0·17 nmol/l (1·19 ± 0·13 ng/ml) at the start of the study and did not change significantly during the experiment. The average daily dose of digoxin was 0·30 ± 0·06 mg. In terms of serum digoxin values and daily digoxin doses our findings are in good agreement with other recent studies (Beller *et al.*, 1971; Carruthers, Kelly, and McDevitt, 1974).

In this setting 6 out of 12 patients developed cardiac arrhythmias fulfilling the criteria of digitalis toxicity. The arrhythmias occurred at serum digoxin levels which are usually not associated with toxic manifestations and were apparently precipitated by the development of chronic hypokalaemia and potassium loss.

There is evidence that *acute* hypokalaemia in patients given digitalis may provoke such arrhythmias as well after carbohydrate administration which displaces potassium from the extracellular to the intracellular phase as after potassium loss during haemodialysis (Page, 1955; Lubash *et al.*, 1959; Kunin, Surawicz, and Sims, 1962). The mechanisms of interplay between digitalis, hypokalaemia, and potassium loss are not clear, however. While in earlier dog experiments, acetyl strophanthidin produced rhythm disturbances at a lower dose after acute hypokalaemia induced by glucose and insulin infusion or haemodialysis than in normal dogs (Lown *et al.*, 1952; Kleiger *et al.*, 1965), this pattern was not reproduced in a recent study in acutely hypokalaemic dogs where digoxin was infused until atrioventricular dissociation occurred (Binnion, 1975). There is evidence that acute reduction of extracellular potassium concentration increases the ability of the myocardium to take up circulating digoxin (Cohn, Kleiger, and Harrison, 1967; Prindle *et al.*, 1969). However, the myocardial concentration of digoxin appears to be the same in normal and in acutely hypokalaemic dogs at the time of digitalis induced ventricular tachycardia or atrioventricular dissociation (Binnion and Das Gupta, 1974; Binnion, 1975).

Although *chronic* hypokalaemia and potassium loss induced by diuretics as found in the present study are generally accepted as being able to sensitize the myocardium to the arrhythmogenic effects of digitalis in man, the available evidence for this assumption is scanty (Callahan *et al.*, 1952; Lown *et al.*, 1952; Jorgensen and Sorensen, 1970; Salvador *et al.*, 1970; Binnion, 1975; Poole-Wilson, Hall, and Cameron, 1975). Moreover, an animal experimental model, similar to the patient on chronic digitalis and diuretic therapy, has never been produced. In dogs with chronic hypokalaemia and potassium deficiency induced by dietary restriction of potassium and/or diuretics, an increased sensitivity of the myocardium to acute loads of acetyl strophanthidin or of digoxin could not be demonstrated (Kleiger *et al.*, 1965; Binnion, 1975). It may be concluded, however, that our findings are in keeping with the view that chronic hypokalaemia and potassium loss may sensitize the myocardium to digitalis in man.

In terms of electrophysiological mechanisms the appearance of cardiac arrhythmias in this setting can be explained by an increased automaticity of lower pacemakers and by a decreased atrioventricular conduction induced by digoxin in a sensitized myocardium (Surawicz and Gettes, 1971). However, the alternative possibility that the arrhythmias are induced by hypokalaemia alone must also be considered.

In the present series the degree of potassium depletion induced is reflected by the slow and gradual decrease of serum potassium of 1 mmol/l and by an overall potassium loss of 204 mmol or 11 per cent of body potassium. As shown in Tables 2 and 3 the relative loss of potassium was larger from the extracellular than from the intracellular phase, resulting in a rise in the intra-/extracellular potassium gradient for the whole body. Our findings stress the significance of hypokalaemia as a factor in the alterations in the intra-/extracellular potassium gradient, as pointed out by other authors (Surawicz and Gettes, 1971). An even larger increase is found when the myocardial intra-/extracellular potassium gradient is calculated on the assumption that the intracellular concentration of the myocardium remains unchanged during the study (Bolte, 1973; St. George *et al.*, 1955; Hall and Cameron, 1974). The electrophysiological effects of a rise in the intra-/extracellular gradient are an increased automaticity of ectopic pacemaker activity and a decreased atrioventricular conduction similar to the actions of digitalis.

In clinical experience atrial and ventricular premature beats or rhythms induced by hypokalaemia are described in patients, not on digitalis, with an incidence ranging from 20 to 40 per cent. Higher frequencies are found in patients with organic heart disease and in those given digitalis (Surawicz *et al.*, 1957; Weaver and Burchell, 1960; Davidson and Surawicz, 1967). In our series arrhythmias were observed in 50 per cent during one week of study, and a higher incidence might have been expected with a longer period of study. A comparison between the incidence in our series and in earlier reports is difficult because of the differences in the settings studied and in methods used. Consequently, the question remains undecided whether the arrhythmias are caused by hypokalaemia or are caused by a combined effect of changes in potassium balance and of digoxin.

From a clinical point of view, however, the important fact is that hypokalaemia can precipitate cardiac arrhythmias in patients receiving maintenance digoxin therapy. It is necessary, therefore, to ensure the maintenance of normal potassium balance during long-term digitalis therapy.

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Intermittent bundle-branch block in patients with accessory atrio-His or atrio-AV nodal pathways

Variants of the Lown-Ganong-Levine syndrome

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Intracardiac electrophysiological studies were performed in two patients with a documented history of repetitive supraventricular tachyarrhythmias. Case 1, with short PR interval and narrow QRS complexes had a short AH interval and intermittent right bundle-branch block. Thus the short PR wide QRS syndrome is not always a result of the Wolff-Parkinson-White syndrome but can also be seen in the Lown-Ganong-Levine syndrome coexisting with bundle-branch block. Case 2, with normal PR and AH at the lower limits of normal, showed the dual pathway response to atrial pacing that can occur in patients with Lown-Ganong-Levine syndrome. He also had tachycardia-dependent right bundle-branch block and left posterior hemiblock.

Therefore, neither the short PR interval nor the narrow QRS complexes characterized these forms of pre-excitation. The constant features were, from the clinical viewpoint, the occurrence of repetitive supraventricular tachyarrhythmias, and electrophysiologically the abnormal response to atrial stimulation.

Specialized conducting system studies have implied that patients with short PR intervals, narrow QRS complexes, and repetitive supraventricular tachyarrhythmias have a form of pre-excitation characterized by the presence of an accessory atrio-'low' AV nodal or atrio-His bundle conduction pathway (Durrer, Schuilenburg, and Wellens, 1970; Castellanos *et al.*, 1971, 1975; Coumel *et al.*, 1972; Bisset *et al.*, 1973; Krishnaswami and Geraci, 1974). However, it is not known with certainty whether these pathways are extranodal (bypass tracts) or intranodal. In two recent histopathological studies of the short PR narrow QRS syndrome, accessory atrio-His pathways were found which were different from those described by James (Anderson *et al.*, 1973; Brechenmacher *et al.*, 1974).

Although attention has been focused on the duration of the PR interval and QRS complex the electrophysiological identification and recognition of these pathways rests on the presence of a short AH interval (or one at the lower limits of normal), and on the abnormal behaviour of this interval during atrial stimulation (Caracta *et al.*, 1973; Castellanos *et al.*, 1975; Denes, Wu, and Rosen, 1974). The present communication emphasizes the fact that narrow QRS complexes are not essential for the diagnosis of these types of accessory pathway (Narula, 1975).

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Subjects and methods

The two patients reported here were referred to the cardiovascular laboratory for electrophysiological evaluation because of a documented history of repetitive supraventricular tachyarrhythmias. His bundle electrograms were recorded, and atrial pacing at increasing rates and with the extra stimulus method was performed as previously described (Castellanos *et al.*, 1971). The procedure was explained, and consent obtained from the patient.

Definitions

PA interval: conduction time from the area first depolarized by the sinus node to the low right atrium in the vicinity of the AV node.

StA interval: conduction time from the paced (atrial) site to the low right atrium in the vicinity of the AV node.

AH interval: conduction time from low right atrium (close to the AV node) to His bundle. Because of the nature of the underlying electrophysiological abnormalities in the two patients studied this interval was not necessarily an index of 'normal' AV nodal conduction time. An AH interval of 50 ms or less was classified as short, and one of 50 to 60 ms was at the lower limit of normal.

HV interval: His Purkinje conduction time.

The term 'accessory pathway' will be used to refer to an abnormal electrophysiological atrio-'low' AV nodal or atrio-His communication regardless of its anatomical location.

Case reports

Case 1

This 48-year-old hypertensive man had a 4-year history of repetitive supraventricular tachyarrhythmias for which no extracardiac cause had been found. His bundle electrograms recorded during sinus rhythm showed shortening of the PR and AH intervals (115 ms and 40 ms), with normal PA and HV intervals (Fig. 1). QRS duration was 90 ms. Early in the study the patient developed transient complete right bundle-branch block without any change in the duration of the AV conduction intervals (Fig. 2). Thus, at this time, the patient had a short PR interval with wide QRS complexes.

High right atrial stimulation at increasing rates produced an AH increment of only 40 ms at a cycle length of 300 ms (200/min). AH Wenckebach occurred at a stimulation rate of 225/min from high right atrium and at a rate of 250/min from coronary sinus (Fig. 3). This response is abnormal (Castellanos *et al.*, 1971; Coumel *et al.*, 1972; Caracta *et al.*, 1973).

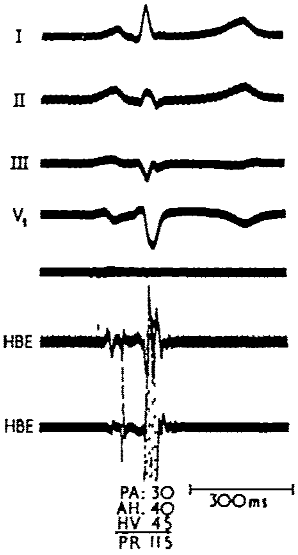

FIG. 1 *Case 1. Sinus rhythm with short PR interval, short AH interval, and narrow QRS complexes. Abbreviations are conventional. HBE=His bundle electrographic lead. Whenever the HBE leads are shown the top and bottom ones were obtained with electrodes 11 and 1 mm apart, respectively. All values are expressed in ms. Paper speed was 100 mm/s.*

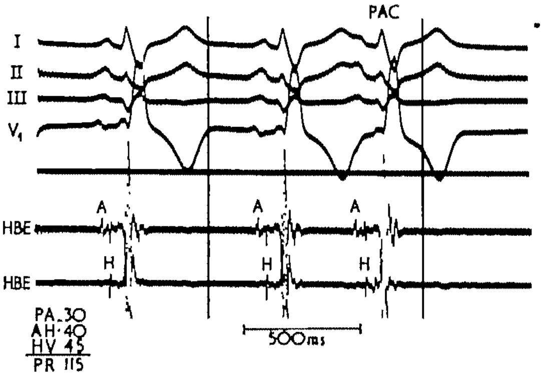

FIG. 2 *Case 1. Sinus rhythm with short PR interval, short AH interval, and wide QRS complexes (right bundle-branch block). HRA=high right atrial bipolar electrographic lead; PAC=spontaneous premature atrial contraction.*

Pacing with the extra stimulus technique showed practically no change in the H_1–H_2 intervals as the A_1–A_2 intervals were decreased from 700 to 405 ms. At shorter coupling intervals the H_1–H_2 interval increased by up to 100 ms until the effective refractory period of the AH tissues was reached.

Premature stimuli delivered to the coronary sinus at coupling intervals of 225 ms resulted in a prolonged bout of atrial fibrillation (Fig. 4). The ventricular rates varied between 200 and 250/min. At times the supraventricular impulses were conducted either with a 'complete' left bundle-branch pattern (Fig. 5; first part of Fig. 6) or

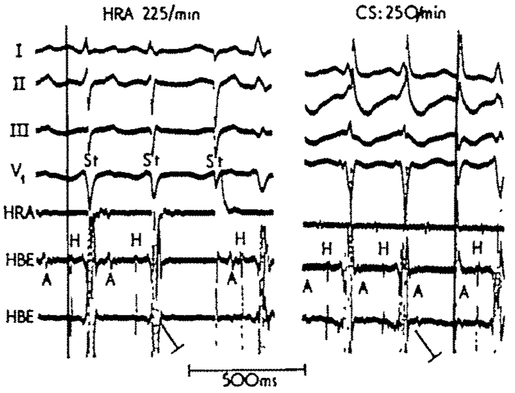

FIG. 3 *Case 1. Abnormal response to atrial stimulation at increasing rates. Wenckebach phenomenon occurred at a rate of 225/min from high right atrium (left) and 250/min from coronary sinus (CS) (right).*

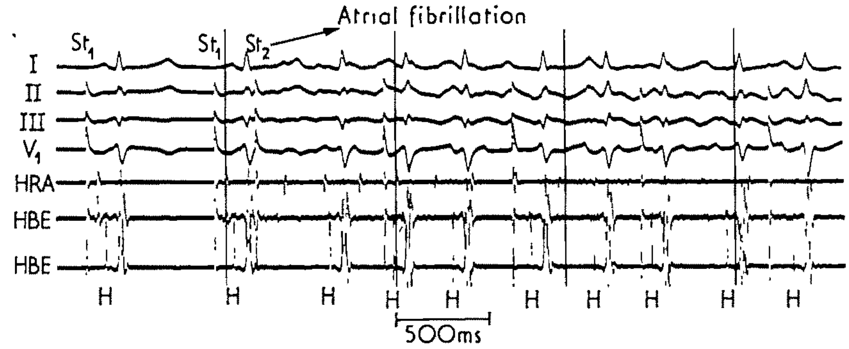

FIG. 4 *Case 1. Atrial fibrillation triggered by premature (St2) impulse. St1 = driving stimulus. His bundle deflections are best seen in the lower HBE lead, which shows less interference from fibrillatory ('f') waves.*

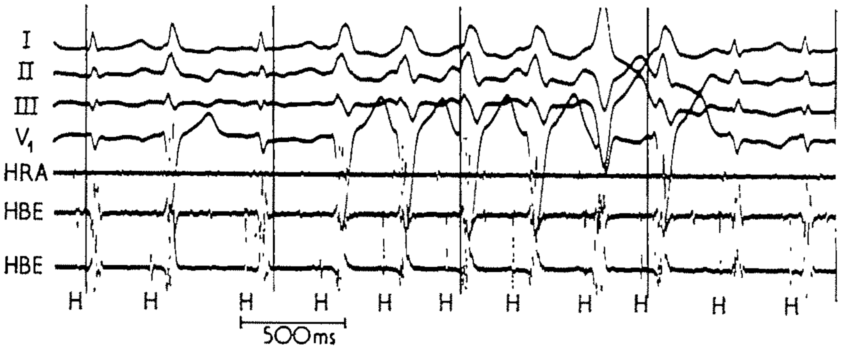

FIG. 5 *Case 1. Atrial fibrillation with functional 'complete' left bundle-branch block. His bundle electrograms are best seen in the lower HBE lead, which showed less interference from 'f' waves.*

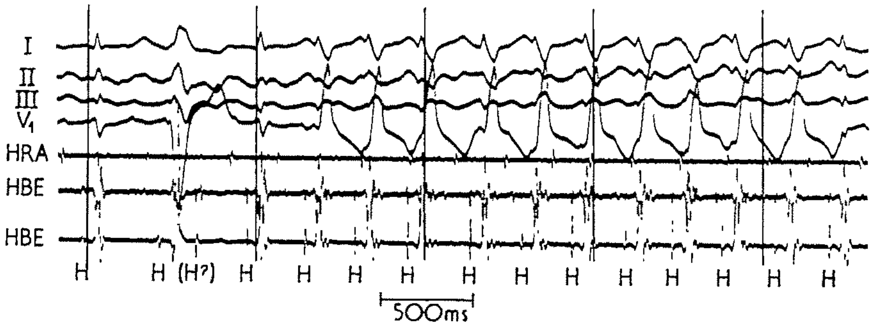

FIG. 6 *Case 1. Atrial fibrillation with functional left and right bundle-branch block. His bundle electrograms are best seen in the lower HBE lead which showed less interference from 'f' waves. The right bundle-branch block morphology is similar to that seen in Fig. 2.*

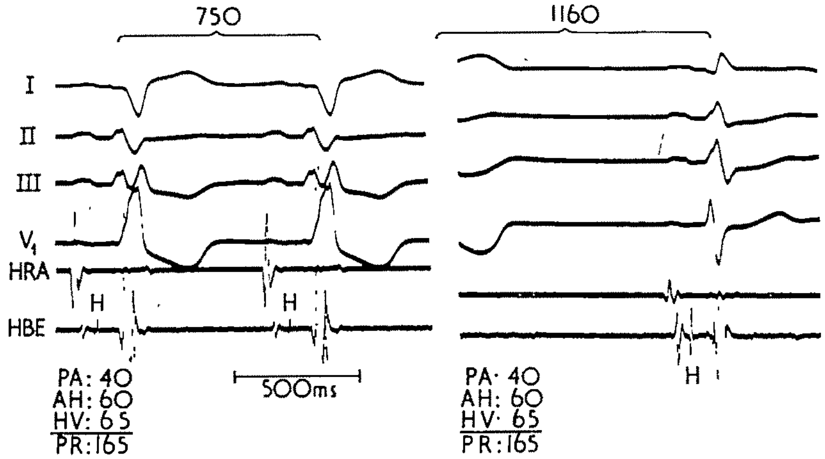

FIG. 7 *Case 2. Sinus rhythm and normal PR interval with AH interval at the lower limit of normal. Tachycardia-dependent 'complete' right bundle-branch block and left posterior hemiblock were present when the RR interval was 750 ms (left). The bifascicular block disappeared when the RR interval increased to 1160 ms (right). The duration of the AV conduction intervals was the same whether bifascicular block was or was not present.*

with a 'complete' right bundle-branch block morphology similar to the one seen in Fig. 2 (last part of Fig. 6).

Clear-cut H deflections were recorded preceding the corresponding QRS complexes. This was more obvious in the His bundle electrographic lead mounted at the bottom of Fig. 4, 5, and 6, which showed no interference from 'f' waves.

In conclusion, this patient with short PR and AH intervals and repetitive supraventricular tachyarrhythmias had sinus rhythm with intermittent right bundle-branch block and paroxysmal atrial fibrillation with functional bilateral bundle-branch block.

Case 2

A 52-year-old man with old anterolateral myocardial infarction had a three-year history of palpitations caused by repetitive supraventricular tachyarrhythmias. Right bundle-branch block with left posterior hemiblock occurred at sinus rates greater than 62/min (Fig. 7, left). However, this bifascicular block disappeared when the cycle length exceeded 960 ms (Fig. 7, right). The duration of conduction intervals was the same regardless of the presence or absence of wide QRS complexes. At both heart rates the PR interval was normal (165 ms) and the AH interval was at the lower limits of normal

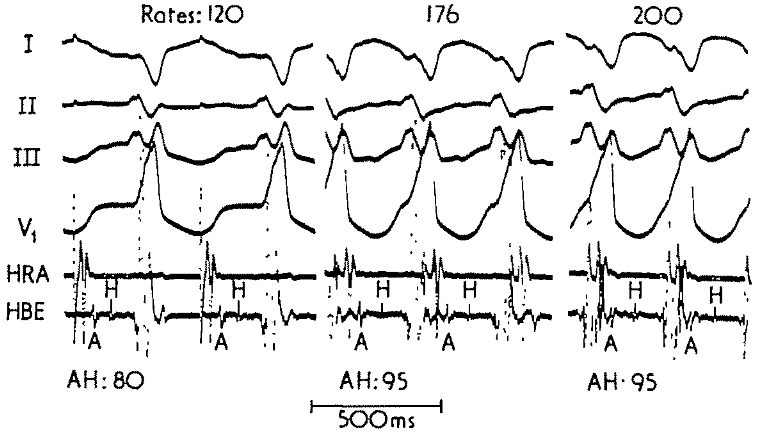

FIG. 8 *Case 2. Atrial stimulation at progressively higher rates produced an increase of the AH interval of only 15 ms from rates of 120/min (left) to 200/min (right). Total AH increment (compared with sinus rhythm, Fig. 7) was 35 ms.*

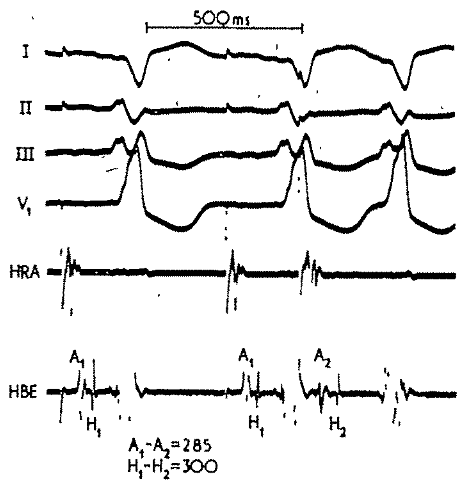

FIG. 9 *Case 2. Pacing with the extra stimulus technique showing that at a relatively short A_1-A_2 interval (285 ms) the H_1-H_2 interval only measured 300 ms.*

(60 ms). The HV interval was definitely prolonged (65 ms). The conduction delay most probably occurred in the His bundle (distal to the site from where the H deflection was recorded) since the HV interval did not shorten when the bifascicular block disappeared.

Mid-right atrial pacing at increasing rates showed that the AH interval increased by only 15 ms with increasing rate from 120/min to 200/min (Fig. 8). The total AH increment (compared with sinus beats in Fig. 7) was only 35 ms, and was therefore less than normal according to Caracta *et al.* (1973). The cycle length at which HA Wenckebach appeared could not be determined since pacing was not performed at rates higher than 200/min.

Pacing with the extra stimulus technique was performed using a driving cycle length of 615 ms. At A_1–A_2 intervals ranging from 600 to 300 ms the H_1–H_2 intervals were almost identical (Fig. 9). This abnormal response indicates that A_2 was not much more delayed than A_1. However, a sudden increase in H_1–H_2 to 410 ms occurred when A_1–A_2 was decreased to 280 ms (Fig. 10). Apparently the effective refractory period of the accessory pathway was reached, the impulse now being conducted through the AV node (dual pathway response) (Denes *et al.*, 1974). Short runs of atrial flutter were seen at this A_1–A_2 interval (Fig. 10). As in Fig. 7, the right bundle-branch block and the left posterior hemiblock disappeared at an RR interval greater than 960 ms (last QRS complex).

In summary, this patient with normal PR interval and intermittent bifascicular block had repetitive supraventricular tachyarrhythmias. Though the AH interval was only at the lower limits of normal the response to pacing was abnormal.

Discussion

Case 1 is an example of the syndrome described by Clerc, Levy, and Cristesco (1938) and Lown, Ganong, and Levine (1952), having a short PR interval, narrow QRS complexes, and repetitive supraventricular tachyarrhythmias. The results of the specialized intracardiac studies were similar to those reported by other authors, who found that the AH interval was short and that atrial pacing at increasing rates failed to produce the expected degree of AH prolongation, or that dual pathways were present (Caracta *et al.*, 1973; Denes *et al.*, 1974; Durrer *et al.*, 1970; Castellanos *et al.*, 1971,

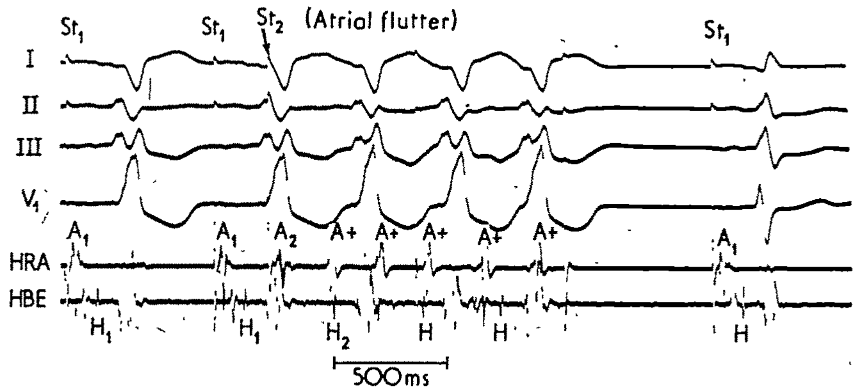

FIG. 10 *Case 2. Short run of atrial flutter (with an atrial rate of around 300/min) produced by a premature stimulus (St_2). Note that the H_1-H_2 interval was significantly longer than the A_1-A_2 interval. The bifascicular block disappeared after the end of the arrhythmia because of the corresponding increase in the RR interval.*

1975; Coumel *et al.,* 1972; Bisset *et al.,* 1973; Krishnaswami and Geraci, 1974). On the other hand in the cases of Mandel, Danzig, and Hayakawa (1971), it was the HV interval, not the AH, which was shorter.

In general the majority of authors accept that the short PR narrow QRS complex syndrome can be explained by the presence of an accessory pathway short-circuiting all or most of the area where the 'normal' AV nodal delay occurs. Yet, it has not been determined whether (in patients in whom specialized electrophysiological studies have been performed) the accessory pathways were extra- or intra-AV nodal. However, in a case with short PR, narrow QRS, and atrial flutter with 1:1 AV conduction, histopathological studies revealed the presence of an atrio-His bypass different from those described by James (Brechenmacher *et al.,* 1974).

Case 1 had intermittent right bundle-branch block during sinus rhythm (Fig. 2). Since the AV conduction intervals did not change, the resultant surface electrocardiographic pattern was that generally attributed to Wolff-Parkinson-White syndrome, namely short PR interval and wide QRS complexes. Moreover, functional bilateral bundle-branch block also occurred during bouts of atrial fibrillation (Fig. 5 and 6). Therefore, this case did not always fulfil the criteria for the Lown-Ganong-Levine syndrome since one of its features (narrow QRS complexes) was not constantly present (Bisset *et al.,* 1973; Narula, 1975).

These patients are electrophysiologically different from those having ventricular pre-excitation caused by an extra-AV nodal, extra-His bundle bypass (Wolff-Parkinson-White syndrome). The surface electrocardiogram can be misleading when the QRS complexes are wide and the PR interval short, since this pattern can be the result of either the Wolff-Parkinson-White syndrome (in which exclusive Kent bundle conduction occurs) (Castillo *et al.,* 1973) or the Lown-Ganong-Levine syndrome with bundle-branch block (Fig. 2). On the other hand, some patients with the Wolff-Parkinson-White syndrome can have normal PR intervals and wide QRS complexes during atrial pacing (Durrer and Wellens, 1974) or when the pre-excitation is intermittent and the impulses are conducted through the normal pathway with bundle-branch block (Castillo *et al.,* 1973).

Some of the reported patients with short PR intervals and repetitive supraventricular tachyarrhythmias did not have a definitely short AH interval (Caracta *et al.,* 1973; Narula, 1975). For instance, the AH interval measured 70 ms in 8 of the 18 subjects studied by Caracta *et al.* (1973), though in these patients the AH interval did not show the 'normal' increase during atrial pacing at progressively higher rates.

In other cases with repetitive supraventricular tachyarrhythmias and an abnormal response to atrial stimulation (as defined previously) the PR was not short. Three of the patients studied by Caracta *et al.* (1973) had AH and HV intervals of 80 ms and 40 ms, respectively. Addition of the PA interval to those values would result in a PR interval greater than 120 ms. Four of the 15 cases studied by Coumel *et al.* (1972), had PR intervals exceeding 120 ms. Case 2 (Fig. 7 to 10) can be included in this category, but also had tachycardia-dependent 'complete' right bundle-branch block and left posterior hemiblock. Hence, neither the short PR interval nor the narrow QRS complexes characteristic of the Lown-Ganong-Levine syndrome were present in this patient.

The features that Cases 1 and 2 had in common were the history of repetitive supraventricular tachyarrhythmias, and the abnormal response to atrial stimulation.

Addendum

In a recent pathological study *(British Heart Journal* (1975), **37,** 853), Brechenmacher noted an atrio-His bundle tract different from those described by James in a patient with bilateral bundle-branch block.

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Length of main left coronary artery in relation to atherosclerosis of its branches

A coronary arteriographic study

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The relation between the length of the main left coronary artery and the presence of atherosclerosis in its branches or the presence of complete left bundle-branch block was studied by selective coronary arteriography in 43 persons.

The length of the main left coronary artery was found to be significantly shorter in patients with coronary atherosclerosis than in subjects without angiographic evidence of coronary artery disease. In patients with electrocardiographic evidence of complete left bundle-branch block, the length of the left main coronary artery was significantly shorter than that in both previous groups.

In view of these findings, it is suggested that a short main left coronary artery should be considered as a congenital factor predisposing to the development of coronary artery disease. The possible mechanisms leading to atherosclerosis of the left coronary arterial branches in the presence of a short main trunk are discussed.

In recent studies coronary arteriographic findings were related to intraventricular conduction disturbances (Haft, Herman, and Gorling, 1969; Beach *et al.*, 1969; Lewis *et al.*, 1970; Hamby, Tabrah, and Gupta, 1973). A remarkable observation was made by Lewis *et al.* (1970), who noted that a short main left coronary artery was present in a great proportion of patients with complete left bundle-branch block. It was suggested that in the presence of a short main left coronary artery trunk, the initial part of the left anterior descending artery is exposed to unusual stress from systolic kinking, with resulting impairment of the blood supply to the bundle of His. Segments of arteries subjected to systolic kinking are known to be particularly liable to intimal changes and atherosclerosis (Fulton, 1965; Glagov, 1972).

From these observations, it might be supposed that the length of the main left coronary artery is one of the factors that may contribute to the development of atherosclerosis in its branches. The purpose of this investigation was to find out if there is any difference in the length of this artery in patients with and without angiographic evidence of coronary artery disease. Some further data are also presented concerning its length in patients with complete left bundle-branch block.

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Subjects and Methods

The study was based on the coronary arteriographic findings in 43 subjects. The only criterion for inclusion was the satisfactory visualization of the main left coronary artery and its branches.

The patients studied were divided into three groups. The first group included 19 patients without arteriographic evidence of coronary atherosclerosis. Twelve of these had a form of heart disease, usually aortic and mitral valve lesions, leading to left ventricular hypertrophy. The others presented with atypical findings suggestive of coronary artery disease.

The second group included 20 patients with atherosclerotic lesions in the left anterior descending or both branches of the left coronary artery. Two also had left ventricular hypertrophy caused by valvular disease. Stenotic lesions in the left anterior descending artery varied from 50 per cent to complete occlusion in 17 cases; in 3, the obstruction was of a lesser degree. In 13 atherosclerosis was also present in the circumflex branch of the left coronary artery.

The third group contained 4 patients with complete left bundle-branch block. Three of these had atherosclerotic changes in both left coronary artery branches. The fourth had congestive cardiomyopathy without evidence of coronary artery disease.

Selective coronary arteriograms were obtained using cine and/or cut films by Judkins' or Sones' technique. Obstructive lesions were evaluated according to the percentage narrowing of the lumen. The left coronary artery was usually visualized in both right and left anterior oblique projections on a rotating table.

Measurements of the length of the main left coronary artery were made, in the diastolic phase, by at least two observers, one of whom did not know the patient. Usually the estimates of the two observers coincided and when there was disagreement the estimates differed by 1 to 2 mm at most. When the two measurements differed, these were averaged. Errors caused by magnification were corrected by comparing the observed with the known diameter of the catheter used. The length of the main left coronary artery was determined from its origin to the point of its bifurcation into the left anterior descending and circumflex branches in the right anterior oblique projection, as was done by previous investigators (Lewis *et al.*, 1970; Fox, Davies, and Webb-Peploe, 1973; Kronzon, Deutsch, and Glassman, 1974). In cases where two projections perpendicular to one another were available, the spatial length was estimated by using Pythagoras' theorem. Since the course of the main left coronary artery is almost horizontal, the theorem could be applied as follows:

$$V \simeq \sqrt{R^2 + L^2}$$

where V = spatial length, and R and L = length in right and left anterior oblique projections. When the main left coronary artery departs from the horizontal plane, its length is slightly overestimated.

Statistical analysis

Data presented a normal distribution curve with minimal positive skew. Differences between group mean values were tested for their level of significance by using the Student's t test.

Results

The Table shows mean values ± 1 standard deviation, and ranges, of the main left coronary artery in each of the three groups, and the statistical significance of differences between the mean values.

In the group of cases without any arteriographic evidence of coronary atherosclerosis the mean of the main left coronary artery was the longest both in the RAO projection (16·8 ± 4·13 mm) and in space (19·93 ± 3·58 mm).

TABLE *Length of main left coronary artery in three groups of patients*

		No coronary disease		*Coronary atherosclerosis*		*LBBB*
Age	No. of cases	19		20		4
	Mean	49·00		53·5		55·75
	SD	±9·35		±8·27		±4·32
	Range	30–65		34–71		52–63
			P< 0·1		P< 0·25	
Length of main LCA (mm) (RAO)*	No. of cases	19		20		4
	Mean	16·8		10·28		3·75
	SD	±4·13		±2·57		±1·89
	Range	11–26		4·5–13·7		1–5·5
			P< 0·001		P< 0·001	
Length of main LCA (mm) ($\sqrt{R^2+L^2}$)†	No. of cases	13		20		4
	Mean	19·93		13·79		5·01
	SD	3·58		3·7		2·21
	Range	14·8–26·0		8·5–20·7		1·4–7·4
			P< 0·001		P<0·001	

LBBB, left bundle-branch block.
*Length of main left coronary artery measured in right anterior oblique projection.
†Length of main left coronary artery in space, calculated from measurements in both oblique projections.
P, Probability of no significant difference between mean values.

In the group of cases with atherosclerosis of the left coronary artery branches the mean length of the main left coronary artery was significantly shorter than in the previous group both in the RAO projection (10·28 ± 2·57 mm, $P<0{\cdot}001$) and in space (13·79 ± 3·7 mm, $P<0{\cdot}001$).

Finally, in the 4 cases with complete left bundle-branch block the mean length of the main left coronary artery was significantly shorter than in the previous two groups, both in the RAO projection (3·75 ± 1·89 mm, $P<0{\cdot}001$) and in space (5·01 ± 2·11 mm, $P<0{\cdot}001$). Differences in age between the groups were not significant at the 5 per cent level.

The length of the main left coronary artery in individual patients in each group is shown in Fig. 1. Cases with left ventricular hypertrophy are represented by open symbols; the length of the main left coronary artery in these cases does not differ from that in cases without left ventricular hypertrophy. Differences between mean group values remain significant ($P<0{\cdot}0025$) after exclusion of cases with left ventricular hypertrophy.

Figs. 2 and 3 show the coronary arteriograms of two representative cases.

Discussion

The mean length of the main left coronary artery, estimated by coronary arteriography in the right anterior oblique position, as reported by different authors, varies. Lewis *et al.* (1970) reported a length of 12·8 mm, Fox *et al.* (1973) found it to be 9·5 mm, and Kronzon *et al.* (1974) 10·4 mm. In our study the mean length of the main left coronary artery, measured in this way, was 12·4 mm. The measurement of a three-dimensional structure in a single plane, unless parallel to it, will be an underestimate. In order to obtain a closer approximation to actual length, we also estimated the spatial length by using both the right and left anterior oblique projections. The mean length of the main left coronary artery estimated thus was found to be 15·0 mm. In necropsy studies the mean main left coronary arterial length was found by Baroldi and Scomazzoni (1967) to be 13·5 mm. Regardless of the reasons for the discrepancy between the reported mean values in different studies, in any one study the differences between groups are likely to be valid.

A relation between a short main left coronary

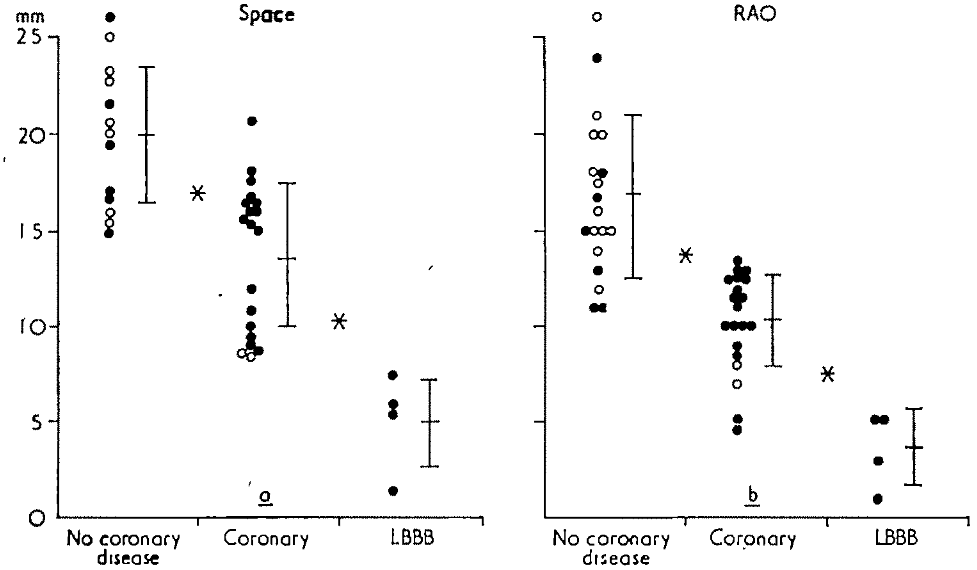

FIG. 1 *Distribution of cases according to the length of the main left coronary artery, in cases without evidence of coronary atherosclerosis, cases with coronary atherosclerosis and cases with complete left bundle-branch block (LBBB).*
(a) *spatial length.* (b) *length in the right anterior oblique projection,* **$P<0{\cdot}001$ between mean values of adjacent groups. Open circles represent cases with left ventricular hypertrophy.*

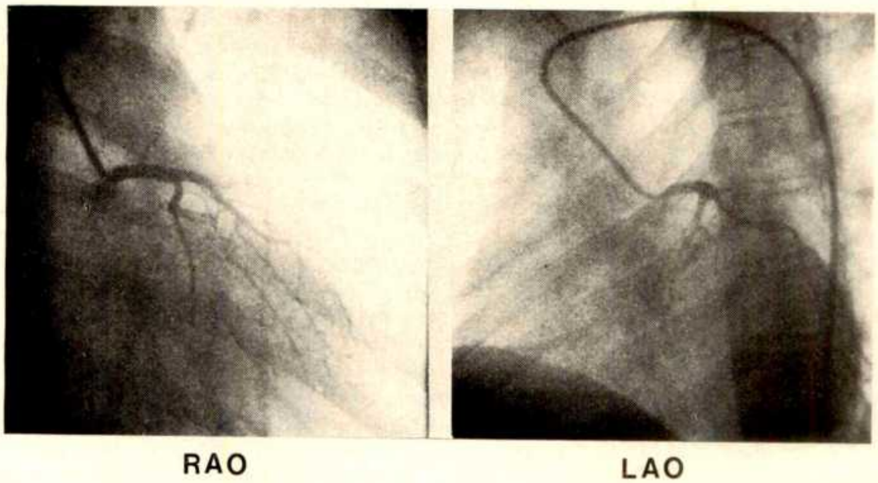

FIG. 2 *Coronary arteriogram of a case without evidence of coronary atherosclerosis. Note the long course of the main left coronary artery. RAO : right anterior oblique projection. LAO : left anterior oblique projection.*

artery and complete left bundle-branch block was first observed by Lewis *et al.* (1970) in 11 out of 12 cases. In these cases the length of the main left coronary artery trunk ranged from 0 to 6 mm (mean 4·5 mm) in the right anterior oblique projection. In another study a main left coronary artery shorter than 6 mm was found in only 2 out of 8 cases with complete left bundle-branch block (Hamby *et al.*, 1973). No information was provided about the length of the main left coronary artery in other patients studied. All 4 patients with complete left bundle-branch block in our study had a main left coronary artery of less than 6 mm in length. In spite of the limited number of our cases, it seems that a complete left bundle-branch block is a common finding among individuals with a short

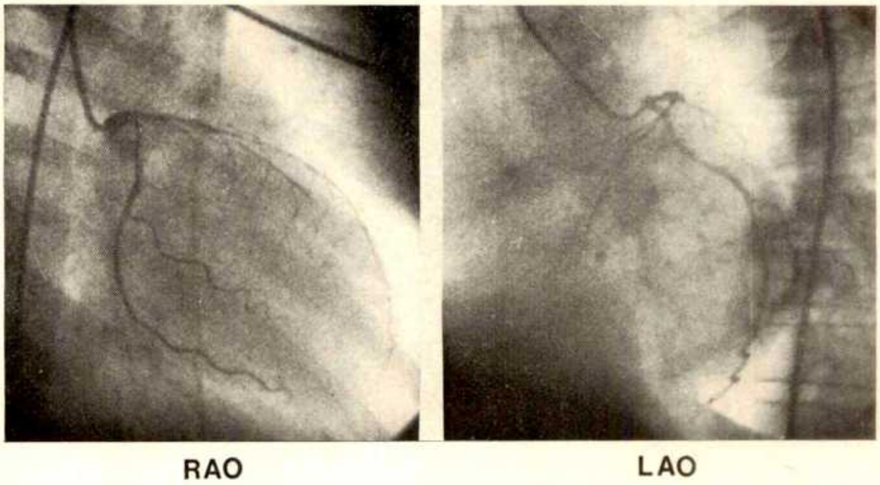

FIG. 3 *Coronary arteriogram of a case with severe atherosclerotic changes in the branches of the left coronary artery. The main left coronary artery is short. Abbreviations as in Fig. 2.*

main left coronary artery but a longer artery does not exclude the occurrence of left bundle-branch block.

The following mechanism has been proposed as an explanation for the development of the left bundle-branch block in the presence of a short main left coronary artery (Lewis *et al.*, 1970). The early septal branches of the left anterior descending artery are normally protected from shearing forces by the relative 'binding down' of the parent vessel. When the main left coronary artery is short, it is followed by a long initial unattached part of the left anterior descending artery which is subjected through systolic kinking to unusual stress. Under these circumstances, the blood flow to the left bundle, provided mainly by the first septal branch of the left anterior descending artery (James and Burch, 1958; Frink and James, 1973), is impaired.

The frequently observed localization of atherosclerotic changes in the initial part (or 'neck') of the left anterior descending artery has also been attributed to systolic motion. This part of the vessel, tethered proximally only by the main left coronary artery and distally by its first septal branch, is subjected to bending or kinking which are believed to enhance the development of atherosclerosis (Fulton, 1965; Glagov, 1972). It is conceivable that the longer the main left coronary artery the shorter the 'neck' of the left anterior descending artery and vice versa. Thus, a long main left coronary artery indirectly protects the 'neck' of the left anterior descending artery by reducing its loose pliable part and consequently its ability to bend during systole. This may be the best explanation for the frequent coexistence of left bundle-branch block and coronary atherosclerosis (Smith and Hayes, 1965; Mulcahy, Hickey, and Maurer, 1968; Lev *et al.*, 1974). If these assumptions are correct a short main left coronary artery regardless of the development of conduction disturbances, would be expected to increase the chance of development of atherosclerosis at the origin of the left anterior descending artery. To our knowledge such a relation has not yet been reported, but the present findings support this hypothesis.

In addition to these views some other mechanisms may be involved in the development of atherosclerosis in the left coronary artery branches in the presence of a short main left coronary artery. According to Poiseuille's equation the drop in pressure and flow in a vessel is directly proportional to its length, while according to Young's formula (Moulopoulos, 1962) the modulus of elasticity and, therefore, its damping effect on pressure and flow changes are also directly proportional to the length of the vessel. Increased pressure, increased flow, and variables related to changes of pressure and flow have been considered as atherogenic hydraulic factors acting mainly on sites of bifurcation, branching, bending, and narrowing (Glagov, 1972; Fry, 1973; Texon, 1974). A long main left coronary artery may, therefore, be expected to protect the bifurcation of the vessel and the proximal part of its branches from the atherogenic effect of mechanical forces by reducing pressure and flow rate and by damping pulsatile pressure and flow. These hydraulic changes would be expected to affect not only the left arterior descending artery but also the circumflex artery.

It is known that in the presence of left ventricular hypertrophy, length and diameter of coronary arteries increase (Linzbach, 1960; Lewis and Gotsman, 1973), and it might therefore be assumed that the observed differences in the mean length of the main left coronary artery could be caused by the high proportion of cases (12 of 19) with left ventricular hypertrophy in the group of non-coronary patients. However, as seen in Fig. 1, there was no difference between cases with left ventricular hypertrophy and those without. A relation between the length of the main left coronary artery and the presence of left ventricular hypertrophy was not found by other investigators (Green, Bernstein, and Reppert, 1967). Furthermore, even after exclusion of patients with left ventricular hypertrophy, the difference in mean length between coronary and non-coronary patients remained significant. It seems that if left ventricular hypertrophy causes some elongation of the main left coronary artery, this effect must be minimal.

From a large variety of suggested aetiological factors in the pathogenesis of atherosclerosis, mechanical stresses and haemodynamic changes resulting from anatomical variations in the structure of coronary arteries have been considered as a *sine qua non*. Other known factors predisposing to the development of atherosclerosis were thought to be only secondary or merely modifying its course (Altschule, 1974). The presence of lipaemia, for example, would enhance atherosclerotic lesions situated at areas where local mechanical stresses are likely to be greatest (Glagov, 1972). Since anatomical structure and distribution of the coronary tree is possibly determined by heredity and development, as are other morphological characteristics, the length of the main left coronary artery trunk should be regarded as an inherited characteristic influencing the rate of development of coronary atherosclerosis.

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Analysis of coronary collaterals in ischaemic heart disease by angiography during pacing induced ischaemia[1]

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Studies were made using ordinary selective coronary angiography and angiography during ischaemia produced by right atrial pacing, on a series of 41 patients with ischaemic heart disease, to examine the response of the collaterals to the ischaemia stimulus. Regional myocardial perfusion was determined under the same circumstances by measuring regional ^{133}Xenon washout curves.

No collaterals were found in 8 patients, none of whom demonstrated collaterals when angiography was repeated during ischaemia. Eleven of the 33 patients with prepacing collaterals (33%) responded to ischaemia with an increase in the collaterals, 16 patients (49%) showed no change, 5 patients (15%) showed a decrease in the collaterals, and one patient exhibited a bidirectional change. Regional myocardial perfusion responses closely paralleled the angiographic changes, yielding suggestive evidence that the collaterals were intimately involved in the enhancement of the flow.

Despite different collateral and flow responses to ischaemia, the data on exercise tolerance, left ventricular end-diastolic pressure, ejection fraction, prevalence of left ventricular asynergy, and the topographic relation between asynergy and collaterals, were largely similar. The data show that in some patients the collateral circulation reacts to ischaemia by enhancement, but the functional significance of this response is obscure.

Coronary collateral circulation has been the subject of great interest for decades (Blumgart, Schlesinger, and Davis, 1940; Zoll, Wessler, and Schlesinger, 1951; Baroldi, Mantero, and Scomazzoni, 1956; Bloor and Liebow, 1965; Fulton, 1965; Paulin, 1967; Gensini and Da Costa, 1969; James, 1970). It is now generally accepted that coronary collaterals are congenitally determined. Large differences in both the number and location of these vessels have been found in mammalian species (Schaper, 1971), but it is not known whether there is such an inherited variation in man. Angiographic studies of ischaemic heart disease have revealed subgroups of patients with varying collateral patterns which can be roughly grouped as follows: 1) no collaterals, 2) some collaterals, and 3) rich collateral networks. There is conflicting evidence relating to the functional significance of these different patterns with regard to their role in preventing ischaemia, influencing left ventricular function, and modifying prognosis (Demany, Tambe, and Zimmerman, 1967; Helfant, Kemp, and Gorlin, 1970; Martinez-Rios *et al.*, 1970; Tuna and Amplatz, 1970; Helfant, Vokonas, and Gorlin, 1971; Miller *et al.*, 1971; Helfant and Gorlin, 1972; Miller *et al.*, 1972; Moberg, Webster, and Sones, 1972; Levin *et al.*, 1973; Banka, Bodenheimer, and Helfant, 1974; Carroll, Verani, and Falsetti, 1974; Handa *et al.*, 1974; Lavine *et al.*, 1974; Williams *et al.*, 1974).

When there is adequate backflow during selective coronary angiography, the radio-opaque material is not forced under pressure into the high resistance coronary arterial circulation, but is merely carried along with the blood stream. Therefore, only collaterals carrying flow are visualized. An additional factor is the resolution power of the current radiographic techniques, limiting adequate visualization to vessels of 100 μ or more. Of the various

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mechanisms which may establish collateral flow in ischaemic heart diseases, effective pressure gradients created by the luminal obstructions evidently play the major role. This is illustrated by the disappearance of the collaterals after successful bypass surgery (Valle *et al.*, 1975). During coronary angiography, ischaemia is avoided if possible. Consequently, visualization of the collaterals may be incomplete in the absence of the postobstruction vasodilatation caused by ischaemia. Thus, conclusions drawn from ordinary coronary angiograms do not necessarily apply to the circumstances prevailing during ischaemia.

The present study compares collateral circulation demonstrated by routine coronary angiography and by angiography during ischaemia induced by right atrial pacing. Additional information was obtained by determining the regional myocardial blood flow under the same circumstances.

Subjects and methods

Forty-one patients who were potential candidates for coronary bypass surgery were studied. The age range was from 29 to 60, with a mean of 47 years. There were 36 men and 5 women. All had angina pectoris responding to sublingual nitroglycerin, but despite treatment with beta-adrenergic blocking agents were unable to work. Each patient had a routine physical examination and biochemical tests, routine chest *x*-ray with heart volume measurements (Jonsell, 1939), and a maximal exercise test on an electrically-braked bicycle ergometer (Elema-Schönander, Sweden). In this test the patient pedalled in the sitting position, and the load was gradually increased without intervening pauses up to the subjective maximum, i.e. the development of angina and/or dyspnoea, requiring the test to be stopped. The electrocardiogram was continuously monitored and recorded once a minute. The exercise tolerance was measured as the total work (TW) in kiloNewton-metres (kNm) representing all the loads accomplished multiplied by the respective times in minutes, as the maximal tolerated load (MaxL, kNm/min), and as the maximal heart rate (MaxHR, beats/min). Treatment with beta-adrenergic blocking drugs was stopped at least one week before the exercise test. Horizontal or downward-sloping ST segment depression occurred in all patients, but was not analysed because some patients were taking digitalis (Frick, Virtanen, and Sävelä, 1972).

The angiographic studies were begun by a left ventricular cineangiogram in the right anterior oblique position using a pig-tail catheter inserted percutaneously, and injection of 60 ml Urografin (60%). This was followed by selective coronary angiography by Judkins' technique. In positioning the catheters in the coronary ostia, special care was taken to avoid occlusion, and adequate backflow was ensured before injection. Both the left and right coronary arteries were injected in three different projections as previously described (Valle, 1973). An Arriflex cine camera was used at a speed of 80 frames/s. In addition, 35×35 cm films were exposed in two projections for each coronary artery. The total number of selective injections was thus 5 per artery. If the patient did not have angina or had only transient and mild pain, he was asked to repeat the study during angina to be caused by speeding up the heart; consent was obtained from every subject. In our laboratory the pacing technique has remained essentially the same as originally described (Sowton *et al.*, 1967), consisting of a gradual increase in heart rate until the development of angina and/or dyspnoea, with ischaemic ST segment changes. The details of this technique combined with coronary angiography have been described (Frick *et al.*, 1974). In brief, a selective injection was made during ischaemia into the coronary artery which gave rise to the collaterals seen on the prepacing angiograms, and cine filming was repeated. Thereafter a second selective injection was made and 35×25 cm films were exposed at a rate of 5 per injection. If the collaterals originated from two arteries, both of these were injected. The amount of contrast material was kept constant in all the injections. The time interval between the prepacing injections and the injections during ischaemia varied from 3 to 10 minutes according to the angina threshold of the patients. The motion blur in the large films caused by the rapid heart action was largely eliminated by exposure times of 10 to 16 ms (and lately of only 2 ms) using the rare-earth oxysulphide screens for large films (3 M-system). Subjective discomfort lasted approximately one minute and the pain was rapidly relieved by stopping pacing. No complications occurred, and the customary bradycardia after the injections was easier to manage with the aid of pacing.

After the coronary angiography, a Paulin catheter was placed into the aortic root just above the aortic valves for the injection of ^{133}Xenon. A bolus of 30 to 50 mCi ^{133}Xenon was injected in 10 ml physiological saline with an Elema-Schönander Cisal injector at a pressure of 5 atm. A Nuclear-Chicago Pho/Gamma III camera connected to an Intertechnique Tridac analyser was used. The gamma images were recorded in digital form in a 64×64 matrix at a rate of one per second and simultaneously on magnetic tape which could be replayed on the memory system of the analyser. The activity was recorded for five minutes, after which right atrial pacing was repeated to induce ischaemia, when a second ^{133}Xenon injection was made followed by data processing similar to that performed after the first injection. The patient was kept in essentially the same position during the whole procedure. From the gamma image four different areas were analysed for myocardial flow: 1) the whole heart, 2) a possible perfusion defect and 3) two reference areas in the vicinity of the perfusion defect (Fig. 1). For the calculation of the washout curve for each selected region, a computer programme in Algol was applied. This finds the highest disappearance constant for 25 seconds from the time-activity curves starting 10 seconds after the injection, as previously described in detail (Korhola, 1974). The time-activity curve analysis system consisted of a Datapoint remote terminal to a time-shared Univac 1108 computer.

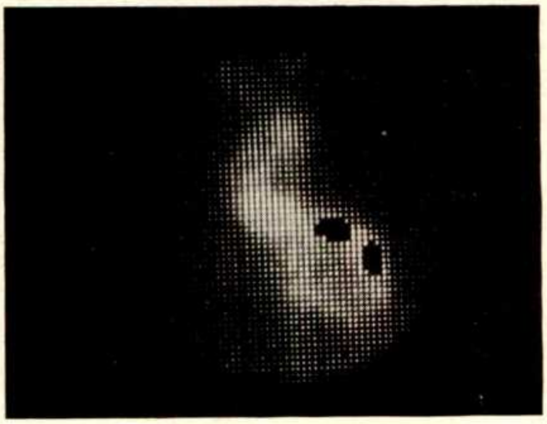


FIG. 1 *Gamma image showing a perfusion defect in the anterior wall. The black spots demonstrate areas selected by a light pen for detailed analysis of regional myocardial perfusion.*

The left ventricular cineangiograms were analysed for regional motion abnormalities (Herman *et al.*, 1967), and ejection fraction was calculated using percentage changes in the diameter from multiple axes if required (Lewis and Sandler, 1971).

The luminal obstructions in the coronary arteries were estimated as percentages. To facilitate the statistical comparison of different subgroups the scoring system of the European Multicentre Study of aorto-coronary bypass surgery was adopted: 0 = no obstruction, 1 = <25 per cent, 2 = 25 to 50 per cent, 3 = 51 to 75 per cent, 4 = subtotal, and 5 = total obstruction. The total score for each patient was used.

In comparing the prepacing and pacing angiograms, both the 35 × 35 cm and the cine films were used and the comparisons were made in the same phase of the cardiac cycle. Attention was paid to the calibre of the large epicardial arteries and to the collaterals, which were classified as follows: 0 = no collaterals, 1 = few collaterals without opacification of postobstructive segments, 2 = collaterals with opacification of a distal segment, and 3 = excellent filling of a postobstructive segment allowing the assessment of the degree of narrowing. The resolution power of the angiographic unit permitted analysis of vessels of 100 μ or more. In assessing the effect of ischaemia induced by pacing, the following criteria were used: no change, increase in numbers, increase in calibre, decrease in numbers, and decrease in calibre, of collaterals. A change was accepted when there was agreement between three independent observers. Visual observations of a change in the calibre of the large epicardial arteries were corroborated by micrometer measurements at equidistant points. The rapid heart rate during pacing was evident in the cine films and excluded a 'blind' analysis of the changes. Student's t-test (one-tailed) was used in determining the significance of the difference of sample means.

Comments on methods

Depending on whether the collaterals originated from the left or from the right coronary artery, 5 or 10 selective injections were made in the prepacing state before the injections during pacing-induced ischaemia. It could be argued that these previous injections resulted in the collateral pattern observed during ischaemia. Analysis of the angiograms obtained during repeated prepacing injections disclosed no systematic difference from the first to the last injection; the collateral pattern remained both quantitatively and qualitatively the same as it appeared in the first exposure. The angiographic studies were begun by an injection of 60 ml Urografin into the left ventricle. The circulatory effects of angiography have been amply documented, and have also been observed in our laboratory (Frick, Heikkilä, and Luomanmäki, 1970). It is conceivable that the almost invariable rise in left ventricular end-diastolic pressure (LVEDP) persisted throughout the study, with added peaks caused by the selective intracoronary injections. The aortic pressure was constantly monitored through the coronary catheters but was not routinely recorded. There were no hypotensive episodes requiring treatment. It is known that little or no change in aortic pressure occurs during right atrial pacing (Sowton *et al.*, 1967; Frick, 1972), making it highly unlikely that this plays a major role in the ischaemic response.

Except in cases with no prepacing collaterals, only the arteries from which the collaterals arose were injected during ischaemia. This was done to lessen the duration of angina, but as a result limited data were obtained on the response to ischaemia of the contralateral artery from which no collaterals arose on the prepacing angiogram. The ideal approach would have been simultaneous selective injections into both left and right coronary arteries.

The regional myocardial flow was determined to obtain supporting data on the functional significance of the response of the collaterals to ischaemia. A detailed analysis of regional myocardial flow in multiple areas is beyond the scope of this paper which is concerned with the demonstration of the dynamic properties of the collaterals. Yet it is essential to understand that a perfusion defect in a scintigram or diffuse heterogeneity of the uptake of the tracer in a particular area can be caused by a reduced flow or diminished viable muscle mass or both simultaneously. Sometimes even an increased flow can be detected in a 'cold spot' resulting from flow via large non-nutrient epicardial arteries. Viable muscle mass did not change between scintigrams made before and during the ischaemia, and the problem encountered in the present study was the difficulty of measuring the 'true' myocardial flow. The present technique assesses the highest flow component and the changes induced by ischaemia in each area. Consequently, the main emphasis in the analysis was on changes in flow rather than absolute values.

An additional difficulty in gamma imaging of the heart lies in the fact that the image is dominated by the anterior wall, the inferior wall being perpendicular to the axis of detection. This has led, for example, to a poor correlation between inferior wall asynergy and data from gamma imaging (Korhola *et al.*, 1975). In the present series gamma imaging was performed on 30 patients. Only two patients had significant lesions in either the left circumflex or the right coronary artery without a concomitant obstruction in the anterior descending artery but both these patients had a cold spot in the anterior wall, and could be analysed in the same way as the other patients.

Results

Angiographic data

There were 8 patients without collaterals in the prepacing angiograms. Three of these had entirely normal coronary arteries and normal contraction patterns of the left ventricle. Two had an isolated 50 per cent stenosis in the left anterior descending artery with normal left ventricular contraction in one, and apical and low anterior hypokinesia in the other. There was also one patient with 90 per cent stenosis in the left anterior descending and 50 per cent stenosis in the right coronary artery (apical akinesia), one patient with 25 per cent stenosis in the right coronary artery (inferior hypokinesia), and one patient with 75 per cent stenosis in the left circumflex and 50 per cent stenosis in the right coronary artery (normal left ventricle). The clinical characteristics are given in Table 1. None of these patients showed collaterals when paced to ischaemia, but in one patient the calibre of the left anterior descending artery was reduced and in three the calibre of both the left anterior descending artery and the left circumflex was increased. Four patients showed no change in this respect.

Thirty-three patients had collaterals in prepacing angiograms. Pacing to ischaemia resulted in three different responses: 1) increase in collaterals, 2) no change, and 3) decrease in collaterals. In the description to follow these groups are labelled positive responders, nonresponders, and negative responders. One patient exhibited a bidirectional change and is analysed separately.

Positive responders This group consisted of 11 patients, 33 per cent of those with collaterals. In all patients the collaterals were feeding segments beyond total occlusions. In 8 patients left ventricular asynergy was detected and was topographically related to the area distal to occlusion and to the site of collaterals; in 2 patients asynergy was absent at the site of collaterals; and in 1 patient with total occlusions in all three arteries akinesia was observed in an apical area not supplied by collaterals, but was absent in the inferior wall supplied by collaterals from the left anterior descending artery and proximal right coronary artery.

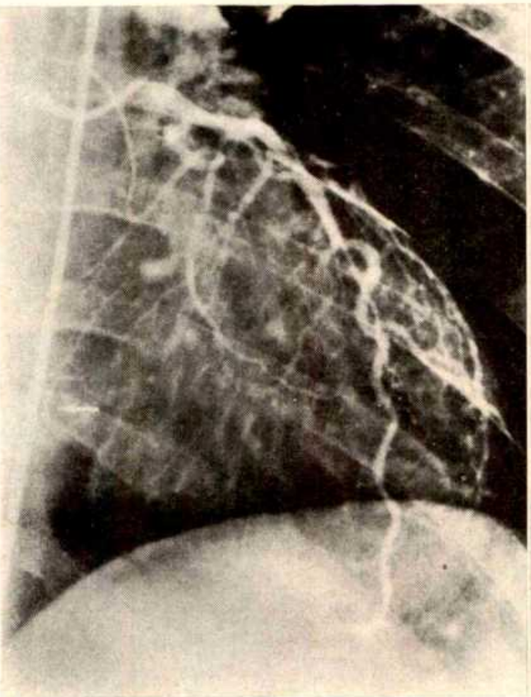
In the prepacing angiogram 7 patients had class 2 collaterals; in 2 of these patients, collaterals remained in the same class but increased in number, and in 5, they increased to class 3 (Fig. 2). Four patients had class 3 collaterals which increased in calibre and in number. In this group 1 patient showed a clear widening of the left anterior de-

TABLE 1 *Clinical features*

	No collaterals	*Prepacing collaterals* *Positive responders*	*Non-responders*	*Negative responders*
No. of patients	8	11	16	5
Men/women	5/3	10/1	15/1	5/0
Age (yr)*	49	47	44	52
	41–55	35–55	29–57	47–60
Duration of angina pectoris (mth)*	49	29	48	31
	24–168	2–84	9–120	12–60
No. of patients with previous infarction	2	3	7	4
	(25%)	(27%)	(44%)	(80%)
No. of patients with:				
1—vessel disease†	2	3	3	0
2—vessel disease	2	3	5	3
3—vessel disease	0	5	8	2
no significant disease	4	0	0	0
Coronary score*	2·5	10·3	8·8	10·6
	0–7	7–15	4–15	8–13

*Mean and range.

†50 per cent obstruction or more.



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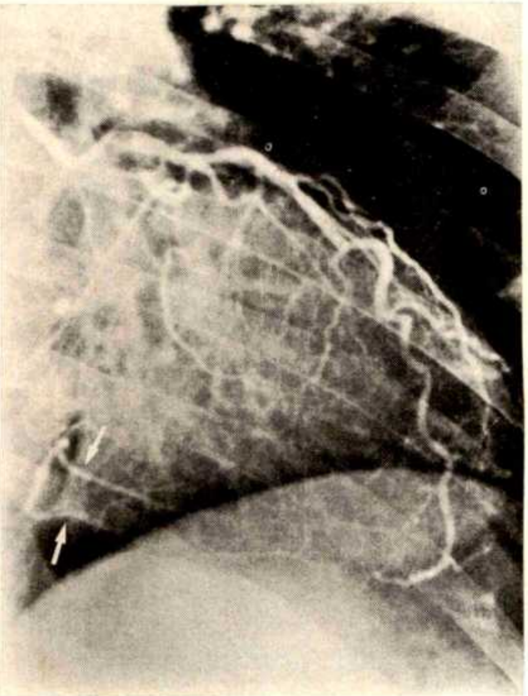

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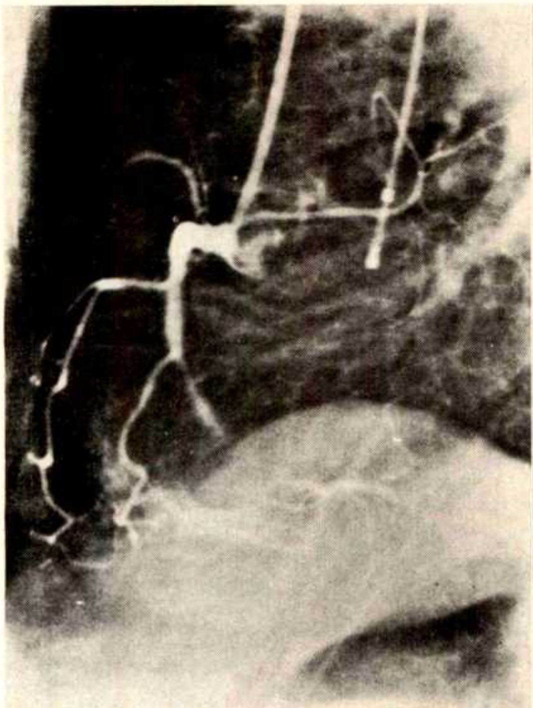

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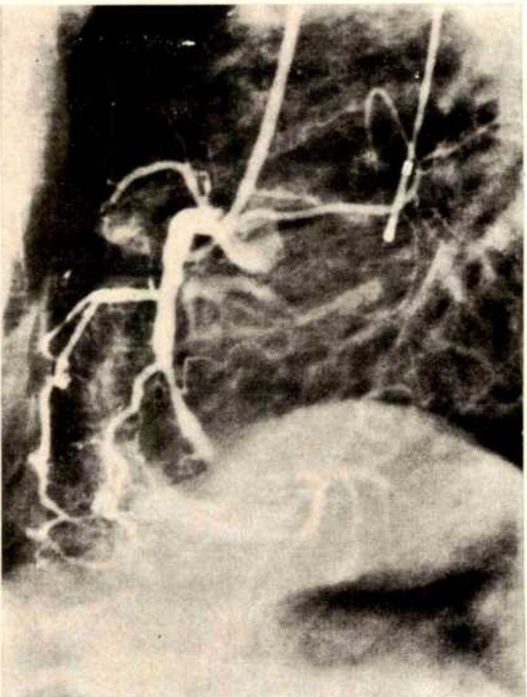

3B

scending and right coronary arteries (Fig. 3) and 1 patient a widening of both the left anterior descending and left circumflex arteries. The clinical features are shown in Table 1 and the circulatory measurements in Table 2.

Nonresponders This group was the largest, comprising 16 patients, 49 per cent of those with collaterals. In 12 patients the collaterals were supplying segments distal to total occlusion, in 4 patients segments distal to 85 to 95 per cent stenosis. In 2 patients no asynergy was found. In 13 of the remaining 14 patients left ventricular asynergy was topographically related to the obstructions and collaterals. The collaterals were essentially unchanged during ischaemia. The pertinent data are shown in Tables 1 and 2.

Negative responders In 5 patients, 15 per cent of those with collaterals, these decreased during ischaemia. Three of the patients had total occlusions with distal segments supplied by collaterals; in 2 patients the obstructions were 90 and 95 per cent. One patient had a normal left ventricular contraction pattern; in 4 patients the left ventricular asynergy was related to the site of obstructions and collaterals. Three patients had class 3 collaterals decreasing to class 2, 1 had class 2 collaterals decreasing to class 1 (Fig. 4), and 1 had class 1 collaterals not seen during ischaemia. One patient showed an additional narrowing of the right coronary artery during ischaemia. Clinical and circulatory data are shown in Tables 1 and 2.

One patient with total occlusions in the left anterior descending and right coronary arteries and a 90 per cent stenosis in the left circumflex artery had class 2 collaterals from the left circumflex to left anterior descending and right coronary arteries and class 3 collaterals from the right coronary to left anterior descending artery. Pacing to ischaemia resulted in increase in number and calibre of collaterals to the distal right coronary artery (inferior hypokinesia). Collaterals from the proximal right coronary to the left anterior descending decreased in calibre.

Clinical and circulatory correlations

The group with no prepacing collaterals differed in several respects from the patients with collaterals. There was no patient with total occlusion of any vessel and none had triple vessel disease. In only 3 was left ventricular asynergy observed. The mean coronary score was lower than that of any of the groups with collaterals ($P < 0{\cdot}001$) and the heart volume was smaller ($P < 0{\cdot}01$). Yet all had angina

TABLE 2 *Circulatory measurements*

	No collaterals	*Prepacing collaterals*		
		Positive responders	*Non-respond.*	*Negative responders*
Heart volume (ml/m^2 BSA)*	408 ± 28	502 ± 19	481 ± 20	473 ± 35
LVEDP (mmHg)*	15·9 ± 2·2	17·5 ± 1·2	18·8 ± 2·8	14·6 ± 1·9
Ejection fraction (%)*	75 ± 4	62 ± 5	66 ± 5	56 ± 7
Pacing rate at ischaemia*	127 ± 5	126 ± 5	127 ± 4	146 ± 8

*Mean ± SE of the mean.

LVEDP, left ventricular end-diastolic pressure.

Conversion factor Traditional to SI units: 1 mmHg ≈ 0·133 kPa.

← FIG. 2 *A) Class 2 collaterals to distal right coronary artery in prepacing angiogram. B) Enhancement of collaterals to right coronary artery during ischaemia induced by pacing.*

← FIG. 3 *A) Right coronary artery in prepacing angiogram. B) Widening of the right coronary artery during ischaemia induced by pacing.*

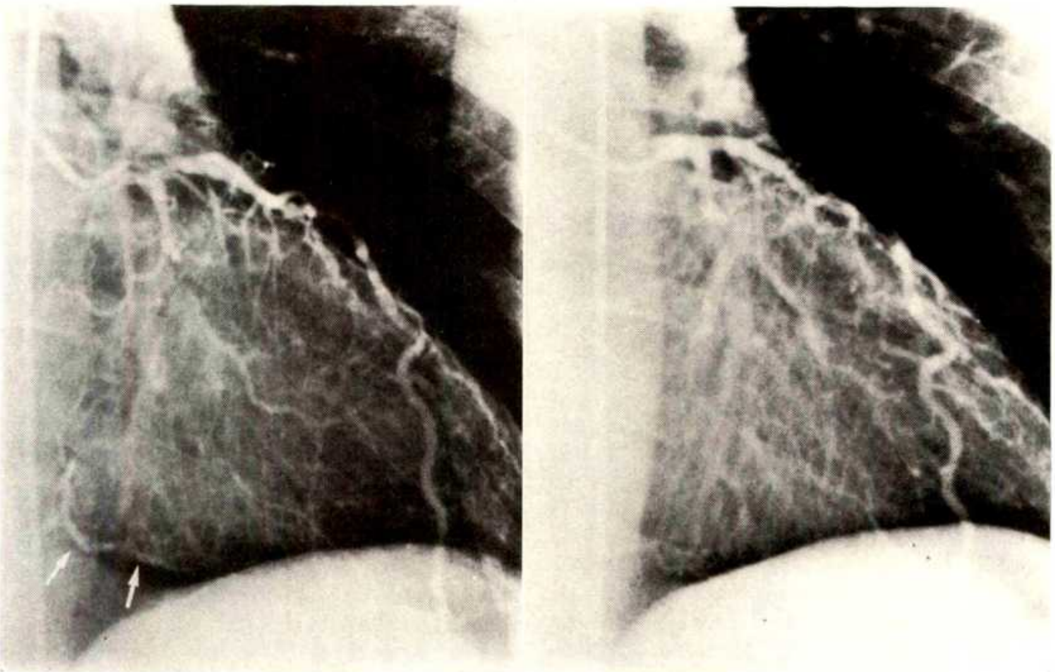

FIG. 4 *A) Class 2 collaterals to distal right coronary artery in prepacing angiogram. B) Regression to class 1 during ischaemia induced by pacing.*

pectoris and ischaemic ST segment changes during the maximal exercise test and were evaluated as candidates for coronary bypass surgery. The duration of angina pectoris was not shorter than that of the other groups (Table 1), and the LVEDP was similar. The ejection fraction, on the other hand, tended to be higher, in keeping with a greater number of patients with a normal contraction pattern of the left ventricle.

The groups with collaterals and different responses to ischaemia were fairly similar in their clinical and circulatory characteristics (Tables 1 and 2). The only difference was an increasing frequency of a history of previous myocardial infarction, from the positive responders through the nonresponders to the negative responders.

Myocardial blood flow

This was determined in 30 patients, 6 of whom belonged to the group with no prepacing collaterals. Four of the patients in this group exhibited a per-

TABLE 3 *Myocardial blood flow*

	No. of patients	*Prepacing*			*During ischaemia*		
		Whole image	*Cold spot*	*Reference areas*	*Whole image*	*Cold spot*	*Reference areas*
No prepacing collaterals	6	55·8* ±7·6	51·2† ±5·9	60·1 ±11·1	65·0 ±13·4	59·5† ±16·9	65·1 ±16·9
Prepacing collaterals							
positive responders	10	51·3 ±10·1	46·6 ±11·5	53·7 ±20·3	66·2 ±8·8	66·4 ±14·2	79·4 ±15·0
nonresponders	9	57·7 ±7·8	46·0 ±14·4	70·3 ±16·5	65·0 ±10·3	58·5 ±28·4	73·1 ±25·9
negative responders	4	48·3 ±9·1	53·1 ±13·9	54·1 ±10·6	55·0 ±8·3	56·5 ±15·3	56·9 ±14·3

*Flow in ml/100 g per min ± SD. †Only 4 patients.

fusion defect in the scintigram, and all 24 patients with prepacing collaterals in which the scintigrams were made had a perfusion defect. The absolute values for flow before pacing and during ischaemia are given for the different groups in Table 3. The percentage changes caused by ischaemia in the four different areas used in the measurements are given for the various groups in Fig. 5. The data for the two areas in the vicinity of the defect were pooled.

The exceptional case with the bidirectional change showed an increase of 23 per cent for the whole imaged area and a similar increase for the areas in the proximity of the defect. The flow in the cold spot decreased by 5 per cent.

The myocardial flow of the whole heart responded to ischaemia by a mean increase of 29 per cent in the positive responder group, contrasting with the mean increase of 13 per cent in the nonresponder group and 14 per cent in the negative responder group. The difference between the positive responders and the pooled data of the non- and negative responders is significant ($P < 0{\cdot}05$). The mean response of the group without prepacing collaterals was +17·0 per cent.

The flow in the area of the perfusion defect increased in all groups, amounting to +43 per cent in the positive responder group. This did not differ significantly from the responses in the non- and negative responder groups, +27 per cent, and +6·5 per cent respectively, nor from the pooled data of the non- and negative responders. The group with no prepacing collaterals reacted to ischaemia by a mean increase of 16·0 per cent.

The positive responder group showed a mean increase of 48 per cent in the vicinity of the perfusion defect. This was superior to the response of +4 per cent in the nonresponders ($P < 0{\cdot}05$) and +5·5 per cent in the negative responders ($P < 0{\cdot}05$), and the pooled data of the non- and negative responders ($P < 0{\cdot}02$). The group without collaterals responded by a mean increase of 8 per cent.

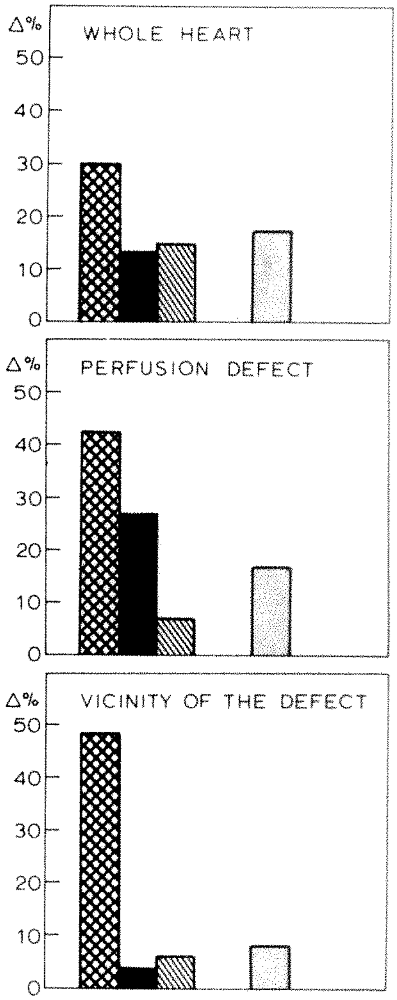

FIG. 5 *Responses of the regional myocardial perfusion to ischaemia in relation to the collateral response. The columns represent from left to right: positive responders, nonresponders, negative responders, and the group without prepacing collaterals.*

Exercise tolerance

The exercise tolerance data are shown in Table 4. The total work was somewhat lower in the group without prepacing collaterals, but this did not differ significantly from the total work in the other groups. The maximum tolerated load and maximum heart rate were similar in all groups except for the negative responses. Three of the 5 women belonged to the group without prepacing collaterals and may contribute to the slightly lower exercise tolerance. the maximum heart rates during physical exercise and during pacing were remarkably similar except in the group of negative responders.

TABLE 4 *Exercise tolerance*

	Total work (kNm)	*Maximal load (kNm/min)*	*Maximal heart rate (beats/min)*
No collaterals	27·5 ± 6·5*	5·3 ± 0·7	132 ± 10
Prepacing collaterals			
positive responders	41·9 ± 11·3	6·3 ± 1·1	131 ± 7
nonresponders	32·7 ± 5·3	5·9 ± 0·5	126 ± 5
negative responders	46·3 ± 7·7	6·6 ± 0·7	105 ± 16

* = mean ± SE of the mean

Discussion

Attempts to establish the implications of the presence of coronary collaterals in ischaemic heart disease have been hampered by the varying severity of coronary atherosclerosis in the groups being compared. The general finding has been the absence of collaterals in patients with mild to moderate luminal obstructions, and this was corroborated in the present small series. This difficulty has been overcome by selecting groups with obstructions of equal severity but different collateral patterns (Helfant *et al.*, 1971; Miller *et al.*, 1971). Using this approach, coronary collaterals have been found to have no protective effect; on the contrary, myocardial ischaemia has been found to be more severe in patients with collaterals (Helfant *et al.*, 1971), and an analysis of the prevalence of left ventricular asynergy has given similar results (Helfant *et al.*, 1970; Miller *et al.*, 1971). These data have been challenged by Levin *et al.* (1973), who concluded that collaterals are vital for preserving left ventricular function. More recent studies have not helped to resolve this difference of opinion. Carroll *et al.* (1974) found no correlation between the quality of collaterals and the number of abnormal left ventricular wall segments, whereas Banka *et al.* (1974) demonstrated with nitroglycerin that asynergic left ventricular wall segments which were supplied by collaterals exhibited higher residual contractile ability than segments without collateral supply. Collaterals were also found to have a protective effect on the occurrence of asynergy during static exercise (Handa *et al.*, 1974).

The present study was undertaken to explore the dynamic nature of the visible collaterals. In a third of the patients with prepacing collaterals, these were increased by induced ischaemia. It is plausible to conclude that in these patients ischaemic vasodilatation increased the pre-existing pressure gradients favouring increased flow. The question of why this did not occur in all patients with prepacing collaterals is pertinent. One possibility is that the collaterals were already maximally dilated and carried flow to their maximal capacity before induction of ischaemia by pacing. It is more likely, however, that opposing forces were in operation. According to postmortem evidence the collaterals in ischaemic heart disease have a preference for intramural and endocardial locations (Schaper, 1971), though fairly large epicardial vessels are also frequently found at necropsy (James, 1970) and by angiography (Paulin, 1967). Ischaemia induced by atrial pacing is followed in a number of patients, but not in all, by an increase in LVEDP (Frick, 1972), decreasing the diastolic epicardial-endocardial pressure gradient and impeding especially the endocardial flow. In the absence of relevant pressure data this mechanism can only be inferred. It is also possible that the patients in the group of positive responders had more epicardial collaterals escaping the effect of rising LVEDP. A third possibility is that there is more fibrotic and scar tissue demanding less flow in patients with no response or a decrease in collaterals by ischaemia. This line of reasoning is supported by the higher prevalence of previous myocardial infarctions in these grousp (Table 1) but opposed by the almost equal ejection fractions (Table 2) and basal flow data (Table 3). There was also no difference between the groups in the anatomical distribution of the asynergic areas and their topographical relation to coronary arterial obstructions and collateral supply.

The concept that collateral flow in ischaemic heart disease is sufficient to maintain only resting energy requirements and is largely insensitive to vasodilatating procedures is based on the pioneering necropsy data of Blumgart *et al.* (1940) and the open-chest dog experiments of Kattus and Gregg (1959). The data of Goldstein *et al.* (1974) on the effect of nitroglycerin and the present findings indicate that human collateral circulation reacts to vasodilatation induced by either nitroglycerin or ischaemia. Direct intraoperative measurements of collateral flow in man have shown large increases after dipyridamole (M. H. Frick and P.-T. Harjola, 1975, unpublished observations). In normal man with healthy coronary arteries, right atrial pacing up to 130/min increases the myocardial flow by some 26 per cent (Knoebel *et al.*, 1970). Right atrial pacing also increases myocardial flow in patients with coronary heart disease (Forrester *et al.*, 1971), the magnitude of the increment depending on the responses in terms of ischaemia (Conti *et al.*, 1970). Measurements of the regional myocardial blood flow in the present study revealed different increments, depending on the response of the collaterals to pacing-induced ischaemia (Fig. 5). A separation of the flow through anastomotic channels and through 'normal' coronaries cannot be made with the present data. However, the similarity of the coronary scores within the groups and the distinct differences in collateral responses to ischaemia afford suggestive evidence that the collaterals are intimately related to the increase in flow. Coronary spasm is occasionally observed in every catheterization laboratory, though not in the present series. The widening of large epicardial arteries in some of the patients during ischaemia shows that vasodilatory capacity is also preserved in some large arteries in ischaemic heart disease.

The group with no prepacing collaterals included three patients with normal coronary arteries. In two of these a Xenon scintigram was made, and one showed a clearcut perfusion defect in the anterior wall. These patients, who had severe angina and a positive maximal exercise test, and were studied as candidates for coronary bypass surgery, presumably represent the subset of ischaemic heart disease in which the classical myocardial oxygen supply-demand mechanism is distorted, leading to unpredictable results of exercise testing and atrial pacing.

The similarity of the data on left ventricular function and exercise tolerance in the three groups, positive, non-, and negative responders, is evidence against the functional significance of the enhancement of collaterals by ischaemia. It is likely that there are no different subjective thresholds for the angina triggered by a large or small ischaemic area, and that angina in itself may be a manifestation of the run-off capacity of collateral circulation as suggested by Guyton (1971). The present data indicate, however, that collaterals are capable of increasing both their size and the amount of flow in response to an appropriate stimulus. The patient with bidirectional response to ischaemia illustrates that internal adjustments occur, evidently favouring areas with greater demands. A 'stealing' effect (Fuster *et al.*, 1974) could not be studied since the contralateral coronary artery was not routinely injected during ischaemia. Though there is evidence that collaterals significantly reduce the mortality in acute myocardial infarction (Williams *et al.*, 1974), and normal values for regional myocardial perfusion under basal conditions have been observed distal to obstructions if well supplied by collaterals (Cannon, Dell, and Dwyer, 1972), the present data suggest that the ability of collaterals to meet the increased metabolic demands of pacing or exercise-induced tachycardia is limited. The disappearance of collaterals after successful bypass grafting (Valle *et al.*, 1975), and the correlation of this phenomenon with improved exercise tolerance after surgery (Frick, Harjola, and Valle, 1975) do not contradict this argument, but are the result of a changed distribution of effective pressure gradients.

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The watershed: a factor in coronary vein graft occlusion

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In 50 patients with one or more aortocoronary saphenous vein grafts investigated by angiography the patency rate of grafts inserted into arteries with a total proximal occlusion was significantly higher than of those inserted into arteries with a proximal stenosis. The interval between operation and investigation in the two groups was similar. In 10 patients with double grafts, one to an occluded and one to a non-occluded artery, there were 7 with one blocked graft, in each case to the non-occluded artery. In the other 3 both grafts were patent. A watershed was shown at angiography in one patient with a graft inserted into a stenosed artery; the distal run-off appeared good, but reflux of the contrast up the coronary artery into the aorta occurred when injecting into the graft, and vice versa. This watershed may operate to a minor degree in all grafts inserted into non-occluded arteries, and by causing stasis at the anastomosis, could explain the higher incidence of graft occlusion in this group. Ligation of the coronary artery proximal to the anastomosis may therefore be necessary to achieve the highest patency rate.

Aortocoronary saphenous vein grafting is now a routine procedure in the treatment of severe angina caused by coronary atherosclerosis. Symptomatic relief is achieved in most cases (Morris *et al.*, 1972), though the effect of the operation on life expectancy is still undetermined. Assessment of graft patency by angiography, carried out in large numbers of patients at varying intervals after operation (Grondin *et al.*, 1972; Flemma *et al.*, 1972; Rösch *et al.*, 1972), shows a patency rate comparable to the rate of symptomatic relief. Of several factors that may contribute to graft occlusion, Grondin *et al.* (1972) found the flow in the graft measured at operation and the size of the grafted artery to be the most important.

Grafting is often followed by a rapid increase in the coronary obstruction proximal to the graft (Malinow *et al.*, 1973; Aldridge and Trimble, 1971), and this occurs more quickly than would normally be expected without surgical intervention (Ben-Zvi *et al.*, 1974). It is assumed to be due to the sudden reduction in flow through the proximal coronary artery which Furuse *et al.* (1972) have shown to occur experimentally.

The study reported here was prompted by an observation in the case of a patient being investigated 24 days after vein graft surgery (Case 9). The graft had been inserted into the right coronary artery, which had a severe proximal stenosis but a good distal run-off. Contrast injected into the graft passed not only into the distal lumen of the coronary artery, which appeared widely patent, but also retrogradely into the proximal lumen, and a little was eventually seen to reflux into the aortic root through the coronary orifice, whereas with contrast injected into the right coronary orifice the opposite was seen to occur—contrast filled the graft retrogradely and refluxed into the aorta.

Though this phenomenon of total flow reversal was clearly caused by the altered haemodynamics induced by the contrast injection it did suggest that the site of the anastomosis could act as a watershed, and that during the normal cardiac cycle there might be some phasic reversal of flow which would predispose to thrombosis. The study was therefore undertaken to see if graft patency was related in any way to the preoperative state of the coronary arteries; for, by this reasoning, grafts inserted into arteries with an incomplete proximal obstruction might be expected to have a higher occlusion rate compared with those inserted into the distal lumen of a totally blocked vessel.

Patients and methods

Out of a total of 215 patients who had one or more aortocoronary saphenous vein grafts inserted at the

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TABLE *Angiographic findings in 50 patients before and after insertion of aortocoronary saphenous vein grafts*

Case No.	*Age (yr)*	*Sex*	*Pre-operative angiogram*	*Postoperative angiogram*		*Graft patency*
				Time interval (dy)	*Coronary artery patency*	
1	24	F	AD 2	244	2	Patent (stenosed)
2	47	M	R 3	148	3	Blocked
3	56	M	AD 3	325	3	—
			R 3		3	Patent
4	40	F	AD 3	444	3	Patent
			R 3		3	Blocked
5	38	M	AD 2	319	2	Blocked
			R 2		3	Patent
6	34	M	AD 2	73	2+	Patent
7	61	M	C 2	97	2+	—
8	46	M	AD 3	127	3	Patent
			C 2		2+	Patent
			R 3		3	Patent
9	48	M	AD 3	24	3	Patent
			R 2		2	Patent
10	38	M	AD 2	236	3	Patent
11	62	F	AD 3	78	3	Patent
			C 2		2	Blocked
12	45	M	AD 3	105	3	Patent
			R 2		2	Blocked
13	58	M	AD 3	6	3	Blocked
			R 3		—	Patent
14	49	M	AD 2	76	2	Blocked
			R 2		3	Patent
15	49	M	R 2	280	3	Blocked
16	62	M	AD 3	122	3	Patent
			R 3		3	Patent
17	66	M	R 3	211	3	Patent
18	52	M	AD 2	22	—	Patent
			C 2		—	Patent
			R 2		3	Blocked
19	56	M	R 2	26	—	Patent
20	40	M	AD 2	141	2	Blocked
			R 1		1	Blocked
21	57	M	AD 2	30	2	Blocked
			R 3		3	Patent
22	42	M	AD 3	22	—	Patent
			C 3			Patent
23	53	F	AD 2	14	—	Patent
			R 3		3	Patent
24	60	M	AD 2	24	—	Patent
			C 3			Blocked
			R 3			Patent
25	45	M	AD 2	35	—	Patent
			R 2		—	Patent
26	46	M	AD 2	21	—	Patent
			C 2		—	Patent
27	42	M	R 3	170	—	Patent
28	49	M	R 2	15	—	Patent
29	57	M	R ?	25	—	Patent
30	52	M	AD 2	29	—	Blocked
			C 2		—	Patent
			R 2		—	Blocked
31	42	M	R 3	28	—	Patent
			C 2		—	Blocked
32	50	M	AD 2	23	—	Patent
			R 3		—	Patent
33	50	M	R 3	21	3	Patent
34	53	M	R 3	14	3	Patent
35	48	M	R 2	468	3	Patent
36	34	M	AD 3	260	3	Patent
			R 2		2	Blocked
37	57	M	R 2	410	3	Patent
38	44	M	AD 1	21	1	Patent
39	64	M	R 2	21	—	Patent
40	57	F	C 2	328	3	Patent
41	55	M	R —	15	—	Patent
			AD —		—	Patent
			C —		—	Blocked
42	54	M	AD 2	14	—	Blocked
			R 3		3	Patent
43	50	M	AD 3	19	3	Patent
			R 2		3	Blocked
44	69	M	AD 2	25	—	Patent
45	59	M	AD 2	87	2	Blocked
			R 2		3	Patent
46	62	M	R 3	337	3	Patent
47		M	AD 2	14	—	Patent
			R 2		—	Blocked
48	54	M	AD 2	29	2	Patent
			C 2		2	Patent
			R 2		2	Patent
49	68	M	AD 2	144	2	Blocked
			C 2		2	Blocked
			R 2		2+	Patent
50	66	M	AD 3	229	3	Patent
			C 2		3	Patent
			R 1		3	Blocked

Abbreviations: AD=left anterior descending coronary artery; R=right coronary artery; C=left circumflex coronary artery; 1=minor irregularity only with no lesion greater than 50 per cent; 2=50 to 90 per cent stenosis; 3=total occlusion; and 2+=stenosis greater compared to preoperative angiogram.

National Heart Hospital between July 1970 and May 1974 50 (45 men and 5 women) were investigated by angiography between March 1971 and January 1975 to determine graft patency Their ages ranged from 24 to 69 years (mean 50). All survivors with a poor clinical result were investigated, a total of 16 patients. The other 34 had a good result and the investigation formed part of a routine follow-up subject to the patient's consent. One graft had been inserted in 20 patients, two grafts in 22 patients, and three grafts in 8, making a total of 88 grafts. The angiograms were obtained within one month of operation in 25 of the patients and after a longer interval in the rest (up to 468 days, mean 214 days). The pre-operative coronary angiogram was not available for study in one patient, and after the postoperative investigation the state of two of the grafts remained uncertain. This left 82 grafts that were known to be either patent or occluded in 47 patients in whom preoperative coronary angiograms were available.

Results (Table)

The overall patency rate of the grafts at the time of investigation was 70 per cent (61 out of 86). There was no significant difference in the incidence of patency between grafts inserted into any one of the three major coronary arteries but, as would be expected a higher proportion of grafts investigated within one month of operation was patent (79%) compared with those investigated after a longer interval (62%). There was, however, a difference ($P < 0 \cdot 05$) in the patency rate between those grafts inserted into previously occluded coronary arteries (87%) compared with those inserted into stenosed but non-occluded arteries (62%), and this difference was more striking ($P < 0 \cdot 025$) in the patients who were investigated more than a month after operation (87% and 50%).

Fate of grafts inserted into occluded coronary arteries

Thirty grafts had been inserted into the distal lumen of arteries which were totally occluded proximal to the site of anastomosis. In all cases the distal lumen had been seen on the preoperative angiogram to fill retrogradely via collaterals. A distal endarterectomy was performed in 6. Fifteen were investigated angiographically in less than one month and 15 at a longer interval (78 to 444 days, mean 286 days). In each group two grafts were occluded at the time of investigation, the other 13 (which included 5 out of the 6 with an endarterectomy) were patent with a run-off in the distal vessel which often appeared wider than on the preoperative angiogram.

Fate of grafts to non-occluded arteries

Fifty-two grafts had been inserted into arteries which were stenosed but not occluded proximal to the anastomosis. The stenosis was greater than 50 per cent in all but 2, and greater than 75 per cent in most of the others. An endarterectomy was performed in 5. Twenty-eight of the grafts were investigated angiographically within one month of operation and 24 after one month (76 to 468 days, mean 242 days). In the early group 20 grafts were patent and 8 occluded; in the late group only 12 of the 24 grafts were patent. In this late group coronary angiograms in the 12 with patent grafts showed that the coronary artery proximal to the graft had become completely occluded in 8, and in 3 the degree of stenosis was definitely greater. The other showed no change in the coronary artery, but there was a severe stenosis in the graft just proximal to the anastomosis. Of the 5 with an endarterectomy 2 grafts were patent and 3 occluded.

Fate of double grafts, one to an occluded and one to a non-occluded artery

Ten patients fell into this group. Three (Cases 11, 12, and 36) were investigated more than one month after the operation (78, 105, and 260 days), in all of whom the graft to the non-occluded artery was blocked and that to the occluded artery patent. Of the other 7 investigated within one month both grafts were patent in 3 (Cases 9, 23, 32) and one of the grafts was blocked in 4 (Cases 21, 31, 42, and 43), and in each instance it was the graft to the non-occluded artery.

Discussion

The inclusion of all survivors with a poor clinical result and only a small proportion of those who did well accounts for the low patency rate of 70 per cent in this series. The figure would undoubtedly have been much higher had more routine investigations been performed. The small number of endarterectomies does not allow a firm conclusion to be drawn, but in this series endarterectomy did not seem to influence graft patency one way or the other.

Insertion of a saphenous vein graft from the aorta into the distal lumen of an incompletely obstructed coronary artery creates a situation where the volume and velocity of flow in each is less than in the distal artery beyond the anastomosis. Furuse *et al.* (1972), in an experimental study, found that partition of flow was dependent on the relative diameter of the artery and graft and on the degree of stenosis in the proximal coronary artery. They also pointed out that the velocity of flow in the graft was inversely proportional to its diameter. Malinow *et al.* (1973) and Aldridge and Trimble (1971) noted that proximal coronary obstruction was often increased after grafting, and there seems general agreement that the reduction in flow is an important contributory factor to this development. The results of this study suggest that in addition there is a significantly lower patency rate of grafts inserted into incompletely obstructed arteries compared with those inserted into arteries with a proximal block. They also suggest that when a graft is inserted into an incompletely obstructed artery eventually either the graft or the artery will become occluded.

In view of the observation in Case 9, where reversal of flow was seen under angiographic conditions, it is tempting to postulate that when grafts are inserted into incompletely occluded arteries the watershed so created at the anastomosis causes stasis during some parts of the cardiac cycle and predisposes to occlusion of the coronary or the graft. If this is so the highest patency rate will be achieved only if the proximal coronary artery is ligated proximal to the anastomosis at the time of operation.

I thank the physicians and surgeons at the National Heart Hospital for permission to publish details of their patients, and Mr Donald Ross for helpful comments. I am also grateful to Dr. Anthony Rickards for statistical advice.

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Symposium on cardiac pathology

The British Cardiac Society held a Symposium on Cardiac Pathology at the University of Birmingham Medical School on 23 September 1975. The President, *J. F. Goodwin*, was in the Chair: the Scientific Secretary was *E. G. J. Olsen* and the Local Secretary was *B. L. Pentecost*. The following papers were given:

Studies of Coxsackie viruses in heart disease

Eleanor J. Bell
Ruchill Hospital, Glasgow, Scotland

Pulmonary veno-occlusive disease

Bryan Corrin
St Thomas's Hospital Medical School, London

Pathology of 'floppy' mitral valve

Michael Davies
St George's Hospital Medical School, London

Myocardial vasculature in normal and diseased hearts

Geoffrey Farrer-Brown
Middlesex Hospital Medical School, London

Pathological aspects of cardiomyopathies with emphasis on the obliterative group

Eckhardt Olsen
National Heart Hospital, London

Case reports

British Heart Journal, 1976, **38**, 201–203.

Wenckebach phenomenon in the exit area from a transvenous pacing electrode

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An unusual type of exit block from a transvenous pacing electrode was recorded in a 63-year-old man with an acute inferior infarct and cardiogenic shock. The pacemaker artefact to QRS interval increased gradually till there was loss of capture. A gradual change from 1:1 pacing rhythm to 4:3 and 3:2 Wenckebach cycles was recorded. This was followed by a fixed 2:1 pacemaker artefact to QRS block.

The Wenckebach phenomenon is commonly recognized as a type of second degree atrioventricular block (Schamroth, 1967). Since the advent of His bundle electrograms this has been demonstrated to occur in the various parts of atrioventricular conduction (Narula and Samet, 1970; Castellanos *et al.*, 1972). Examples of the Wenckebach phenomenon have also been recorded in the bundle-branches (Friedberg and Schamroth, 1969; Franchi, Morace, and Fantini, 1973). The occurrence of the phenomenon in the exit area from a pacemaker is well demonstrated by sinoatrial Wenckebach phenomenon (Schamroth and Dove, 1966). The purpose of this paper is to report an unusual example of the Wenckebach phenomenon occurring in the exit area of an impulse from a transvenous pacing electrode.

Case report

A 63-year-old man was admitted to the coronary care unit at the Royal Melbourne Hospital with a history of transient loss of consciousness and severe retrosternal chest pain. Electrocardiogram on admission showed an acute inferior infarction and complete atrioventricular block, with a nodal rate of 48/min. A temporary bipolar pacing electrode was positioned in the right ventricular apex under fluoroscopy and demand pacing started at a rate of 90/min. The patient's clinical condition deteriorated, he became hypotensive, and finally succumbed in cardiogenic shock.

The Figure shows a continuous lead II of the electrocardiogram recorded in this patient 2 hours before death. All the QRS complexes are identical, and preceded by a pacing artefact. The pacing artefact can be seen in the entire length of the electrocardiogram uninterrupted at a rate of 90/min. The top panel shows regular 1:1 pacing with a first degree of exit block up to R_8. The pacemaker artefact to QRS interval (exit time) gradually increases up to R_8 and the subsequent pacemaker discharge fails to activate the myocardium.

R_{10}, R_{11}, and R_{12}, and R_{15}, R_{16}, and R_{17} clearly show cycles of 4:3 Wenckebach block occurring between the pacing electrode and the myocardium. The interval between the pacing artefact (P) and the QRS in the beginning of the cycles (PR_{10} and PR_{15}) is 80 ms and this exit time increases by the end of the cycle (PR_{12} and PR_{17}) to 120 ms, and is followed by total failure of conduction. R_{13} and R_{14}, and R_{18} and R_{19} are examples of 3:2 Wenckebach cycles in which the exit time increases from 80 ms to 160 ms and the third pacemaker artefact fails to capture the ventricle. Following R_{20} the electrocardiogram shows a regular pattern of 2:1 exit block.

Discussion

Exit block around a pacing electrode has been well recognized (Preston *et al.*, 1966). To our knowledge, Wenckebach phenomenon at this area has not been demonstrated before. This case, therefore, provides an example to delineate the characteristics of a Wenckebach block around an intrinsic pacemaker focus in the ventricle (Schamroth, 1971). The mechanism of this progressive deterioration of conduction is most probably a form of decremental conduction (Krikler, 1974). The degree of conductivity of the exit area is depressed gradually, the conduction changes from 1:1 to 4:3 and 3:2 Wenckebach cycles, and finally settles as a regular 2:1 response.

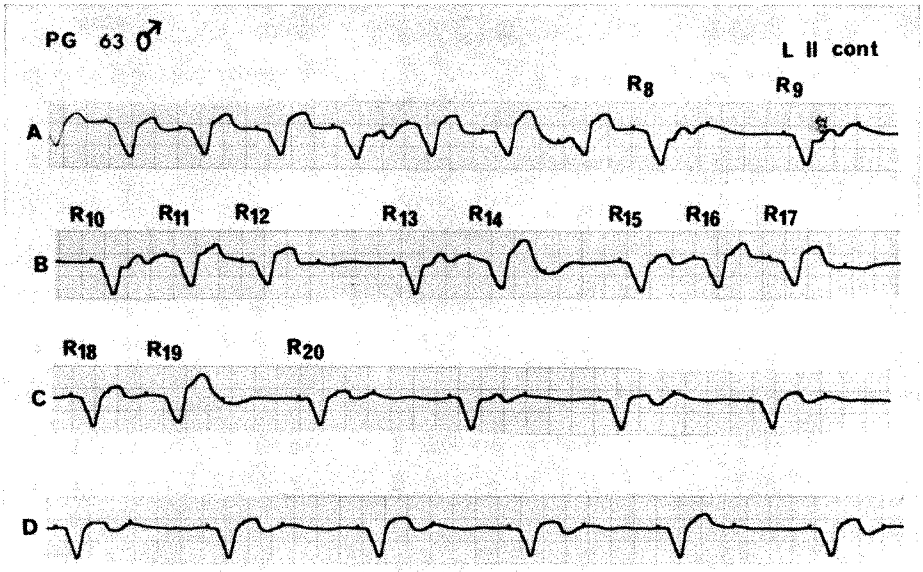

FIG. *Lead II rhythm strip. Panels A, B, C, and D are continuous. See text for description.*

The term 'decremental conduction', however, usually implies a somewhat different phenomenon in electrophysiology (Watanabe and Dreifus, 1968). Both the action potential amplitude and the rate of depolarization are progressively decreased from cell to cell. As a result of this, successive stimuli become weaker and less effective in the course of transmission and finally the impulse fades out when the integrated stimulus strength becomes insufficient to cause a propagated response in more distal and still excitable fibres. Though decremental conduction is commonly seen in the sinoatrial and atrioventricular nodes, it has also been described in the Purkinje system (Hoffman, 1966).

Gradual prolongation of exit time from a pacemaker potential was described by Pick; however, cyclical pattern of Wenckebach phenomenon was not recorded in his case (Pick, 1973). It is probable that the prolonged low output state of the patient with consequent myocardial ischaemia and electrolyte imbalance may have contributed to the genesis of this unusual form of exit block. Cellular hypoxia and disturbances of intracellular potassium concentrates have been shown to delay impulse conduction and cause Wenckebach type of block between Purkinje fibres and contractile myocardium (Alanis, Benitez, and Pilar, 1961; Greenspan, Anderson, and Fisch, 1971).

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Notice

Cardiovascular Nuclear Medicine: Clinical Applications

A symposium will be heard at The Johns Hopkins University School of Medicine on Cardiovascular Nuclear Medicine, on 11 and 12 March 1976. Further particulars can be obtained by writing to Julia C. Burbridge, Office of Continuing Education, Turner Auditorium Building, The Johns Hopkins University, School of Medicine, 720 Rutland Avenue, Baltimore, Maryland 21205, U.S.A.

British Heart Journal, 1976, **38**, 204–206.

Wenckebach phenomenon occurring in the distal conducting system in a young adult

Richard Gray, V. S. Kaushik, and William J. Mandel[1]

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This report describes the case of a young man who presented with right bundle-branch block and second degree atrioventricular block; intermittent episodes of Wenckebach periods were recorded. His bundle electrograms demonstrated progressive prolongation of the HV interval followed by block occurring distal to His. This report emphasizes the fact that the Wenckebach phenomenon as a manifestation of the distal conducting system disease can occur in young adults. The observations lend credence to the concept that Lenègre's disease can occur in young people.

The development of techniques for recording intracardiac electrograms has enabled the clinician to localize more precisely the site of atrioventricular block in man (Damato *et al.*, 1969; Scherlag *et al.*, 1969; Rosen *et al.*, 1970; Narula *et al.*, 1971). The clinical importance of localizing the area responsible for atrioventricular block is that this can be related to the prognosis of the various subgroups of atrioventricular block. Studies using intracardiac recording techniques have established that the majority of patients with second degree atrioventricular block with Wenckebach periods have progressive AH interval prolongation, with the site of block being localized to the area of the atrioventricular junction (type I) (Damato *et al.*, 1969; Narula *et al.*, 1971). In general, these patients have a benign course (Langendorf and Pick, 1968). In contrast, the majority of patients with second degree atrioventricular block of the type II variety appear to have lesions localized in the distal conduction system below the bundle of His (Damato *et al.*, 1969; Narula *et al.*, 1971). These patients with distal conduction system disease appear to have a poor prognosis and require permanent pacemaker therapy (Donoso, Adler, and Friedberg, 1964; Langendorf and Pick, 1968).

In a small group of elderly patients with heart disease, the occurrence of the Wenckebach phenomenon caused by conduction delay below the bundle of His has been suggested by observations using standard electrocardiograms, and documented by His bundle electrograms (Friedberg and Schamroth, 1969; Narula and Samet, 1970; Narula *et al.*, 1971). It is the purpose of this communication to report an instance of symptomatic Wenckebach phenomenon caused by block distal to the bundle of His in a young man.

Case report

A 28-year-old man employed as a foreman at a factory was admitted to hospital for evaluation of recent onset of light-headedness, shortness of breath, and vague substernal discomfort occurring after heavy exertion. The patient stated that he was completely well until one week before admission. He was athletically inclined and did long distance running on a daily basis without symptoms before the recent episode. Family history revealed only evidence of maternal hypertension. Physical examination demonstrated a pulse of 50/min which was regular and a blood pressure of 155/60 mmHg (20.6/8.0 kPa). Pertinent physical findings included a sharply rising carotid pulse with a bifid character and a grade 2/6 midsystolic murmur heard best at the base and left sternal edge.

Chest *x*-ray was within normal limits. Electrocardiogram showed right bundle-branch block with 2:1 atrioventricular conduction (Fig. 1A). A 10-hour Holter monitor recording demonstrated intermittent episodes of Wenckebach periodicity as well as 2:1 atrioventricular conduction (Fig. 1B). Echocardiograms were within normal limits and apex cardiograms did not reveal a double systolic anterior impulse or a prominent a wave.

The patient underwent right and left heart catheterization, left ventriculography, and coronary angiography, all of which were within the normal range. In addition, His bundle recordings were obtained with atrial pacing. The His bundle recordings, obtained during sinus rhythm, demonstrated a normal AH interval (90 ms) and a pro-

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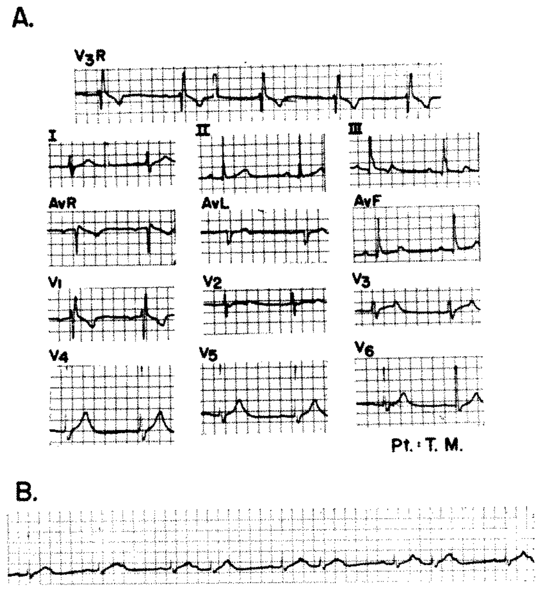

FIG. 1 *Electrocardiogram and rhythm strip during sinus rhythm. Panel A shows the standard electrocardiogram with evidence of 2:1 conduction and right bundle-branch block. Note the rightward shift in frontal plane axis, with clockwise direction suggesting possible posterior fascicular block. Furthermore, the PR interval in the conducted beats is 0.24 s. Panel B shows a representative strip from a 10-hour Holter recording, showing 2:1 conduction alternating with 3:2 Wenckebach periods.*

nounced prolongation of the HV time (175 ms). Atrial pacing at rates of 70/min resulted in prolongation of both the AH (110 ms) and the HV intervals (190 ms). Increasing the heart rate to 80/min by atrial pacing resulted in the development of Wenckebach periods which occurred because of progressive HV delay; block of the sinus impulse occurred distal to the His bundle (Fig. 2).

A permanent QRS-inhibited ventricular demand pacemaker was implanted the day after cardiac catheterization. Subsequent follow-up has revealed no significant recurrence of symptoms.

Discussion

Classification of the type of atrioventricular block has been of great interest to the clinician since the description of various forms of atrioventricular block in the early part of the twentieth century. Nevertheless, adequate therapy was not available for the treatment of advanced forms of atrioventricular block until the introduction of permanent transvenous pacemakers in 1959 (Furman and Robinson, 1959). This led to the need for more accurate assessment of location of atrioventricular block.

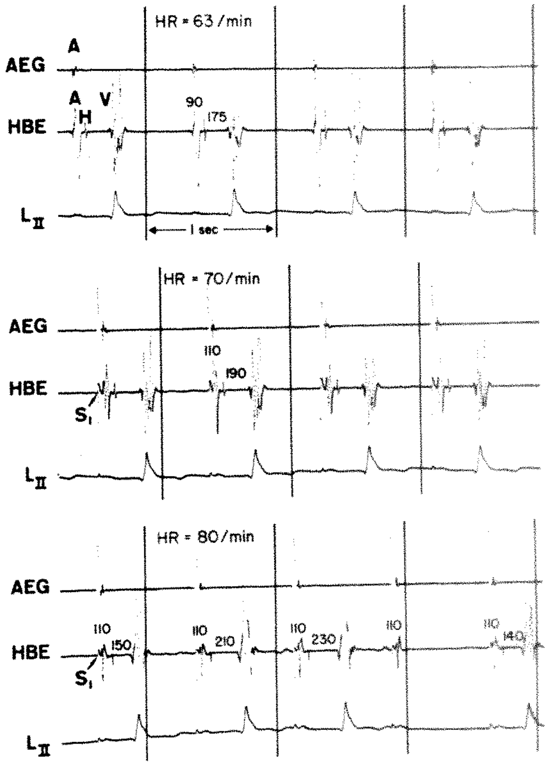

FIG. 2 *His bundle electrogram. The upper panel shows the recording obtained during sinus rhythm at a heart rate of 63 beats/min; a 1 s time calibration is shown at the bottom of the panel. To the left of the panel are shown the abbreviations for the high right atrial electrocardiogram (AEG), the His bundle electrogram (HBE), and the lead II electrocardiogram.* A *signifies atrial depolarization,* H *the His bundle deflection, and* V *ventricular depolarization. Listed above the second complex on the His bundle tracing are the AH interval (90 ms) and the HV interval (175 ms). The middle panel shows the recording obtained during atrial pacing at a rate of 70/min.* S_1 *signifies the stimulus artefact; the AH interval was 110 ms and the HV interval was 190 ms. The lower panel shows the recording obtained during atrial pacing at a rate of 80/min. An example of a 4:3 Wenckebach period is shown with progressive prolongation of the HV intervals with a fixed AH interval (110 ms).*

Introduction of intracardiac recording techniques for use in man now greatly simplifies the characterization and localization of the various types of atrioventricular block (Scherlag *et al.*, 1969). Data accumulated over the past years have shown that, contrary to previously accepted views, various forms of atrioventricular block could occur because of conduction delay in a large number of sites within the atrioventricular conducting system (Damato *et al.*, 1969; Rosen *et al.*, 1970; Narula *et al.*, 1971).

Specific emphasis has been given to the identification of the site of block in patients with second degree atrioventricular block. This was felt to be important by the clinician as, prognostically, Wenckebach periods (type I) have been generally felt to be benign, whereas patients who exhibited second degree atrioventricular block of type II frequently required permanent pacemaker therapy (Langendorf and Pick, 1968). In this context, it has been emphasized that the site of atrioventricular block could be localized from the standard electrocardiogram. Dreifus and co-workers (1971) have suggested that the presence of a narrow QRS generally infers atrioventricular junctional disease, whereas the presence of a wide QRS identifies distal conducting system disease. Additional observations by Dhingra *et al.* (1974a) have indicated that, in general, Wenckebach periods in patients with pre-existing bundle-branch block suggest conduction delay proximal to the His bundle.

Further investigations in patients with second degree atrioventricular block have emphasized that Wenckebach periods, with the site of block being atrioventricular nodal, may be seen in the young patient who is otherwise without evidence of heart disease (Cullen and Collin, 1964; Lightfoot *et al.*, 1973). Nevertheless, second degree atrioventricular block of the type II variety is almost exclusively observed in elderly patients with advanced heart disease (Donoso *et al.*, 1964; Damato *et al.*, 1969; Friedberg and Schamroth, 1969; Narula and Samet, 1970; Narula *et al.*, 1971).

An earlier report described the natural history of a 40-year-old patient who developed intermittent advanced heart block at age 31 (Dhingra *et al.*, 1974b). Their patient was considered to be the youngest patient reported with Lenègre's disease. Therefore, the data obtained in our patient offer support to Dhingra's observation that Lenègre's disease may occur in young adults.

The observations in the present report serve to document: (1) that Wenckebach periodicity can occur in the distal conducting system; (2) that distal conducting system disease (? Lenègre's disease) can be identified in young patients without other identifiable forms of heart disease; and (3) the difficulty in identifying the site of atrioventricular block solely on electrocardiographic criteria.

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‘Supernormal’ phase in hemiblock conduction

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A case is described where the basic sinus rhythm is associated with an advanced degree of left anterior hemiblock. The rhythm is complicated by atrial extrasystoles, associated with a lesser degree of left anterior hemiblock. This paradox of ‘supernormality’ is explained on a critical interplay of differential refractoriness within the divisions of the left bundle-branch.

The ‘supernormal’ phase of conduction is a short period of paradoxically improved conduction which may occur during an early phase in the cardiac recovery cycle. The situation is paradoxical, for the apparent ‘improvement’ in conduction occurs during a short critical period early in the cycle, whereas later impulses are blocked or have greater conduction delays. The term is, in a sense, a misnomer, for it does not imply that conduction is better than normal (Lewis and Master, 1924). Rather, it indicates that conduction appears to be momentarily better than that prevailing for the particular case; and the prevailing state of conduction in these cases is always one of depression. Indeed, the ‘supernormal’ phase of conduction does not occur in the normal heart, but only when conductivity is depressed. In other words, the ‘supernormal’ phase is manifested by a temporary improvement of conduction, which is ‘better’ than could be anticipated under the prevailing circumstances. This ‘improvement’ may take the form of an impulse that is conducted when it should be blocked, or an impulse that is conducted with improved conduction when a longer conduction time or delay could reasonably be expected. When considering the property of conductivity, it can generally be assumed that the earlier the impulse within the cycle, the greater its conduction delay. Any unexplained departure from this relation could, in a sense, be regarded as ‘supernormality’.

The mechanism of many forms of so-called ‘supernormal’ conduction has recently become evident through the elegant experiments and analyses of Moe, Childers, and Merideth (1968). They have shown that the ‘supernormal’ conduction does not necessarily imply ‘supernormality’, nor need it, in fact, represent a paradoxical or anomalous situation. The phenomenon can be explained on the basis of well-established physiological and anatomical principles. These are:

1) Differential refractoriness of atrioventricular nodal tissues, which may affect different longitudinal atrioventricular conduction pathways, or different horizontal or sequential atrioventricular junctional layers.
2) The presence of dual atrioventricular conduction systems.
3) Complex interference within the atrioventricular junctional tissues.
4) Fluctuating vagal discharge.

The ‘supernormal’ phase of conduction can theoretically occur at any site where there is an actual or potential conduction delay. Most reported cases have occurred with conduction through the atrioventricular node – the *‘supernormal’ phase of atrioventricular conduction.* Cases have also been reported of ‘supernormality’ within a bundle-branch – the *‘supernormal’ phase of intraventricular conduction* (Schamroth, 1969). The ‘supernormal’ phase of conduction has even been demonstrated in Bachmann’s bundle of the experimental animal (Childers, Merideth, and Moe, 1968).

The following presentation is an example of the so-called ‘supernormal’ phase of conduction within the divisions of the left bundle-branch, in association with left anterior hemiblock.

Case report

The electrocardiogram (Fig. 1) was recorded from a 34-year-old woman with congestive cardiomyopathy. She was fully digitalized.

The electrocardiogram (Fig. 1) shows a basic sinus rhythm. The P waves are within normal limits. The PP

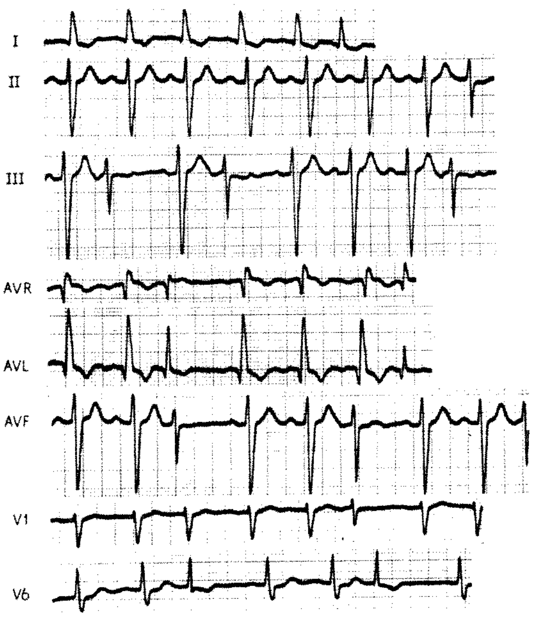

FIG. 1 *Electrocardiogram showing sinus rhythm associated with advanced left anterior hemiblock, and complicated by atrial extrasystoles showing a lesser degree of left anterior hemiblock.*

intervals measure 0.66 s, representing a rate of 91 beats per minute. The PR intervals measure 0.25 s, reflecting first degree atrioventricular block. The rhythm is complicated by atrial extrasystoles. The premature and abnormal P′ waves of these atrial extrasystoles can be seen deforming the distal limb of the preceding T waves. This is best seen in the last beat of standard lead III where the distal limb of the preceding T wave is deformed by a distinct terminal negativity.

The atrial extrasystoles are followed by a QRS complex of slightly different configuration than the beats of the basic sinus rhythm. This is considered in greater detail below. The extrasystoles occur as: the last beat in standard lead I and standard lead II, the second, fourth, and last beats in standard lead III, the third and last beats in leads aVR and aVL, the third, sixth, and last beats in lead aVF, and the third and sixth beats in leads V1 and V6.

QRST pattern of sinus beats

The basic QRS pattern of the sinus beats is one of advanced left anterior hemiblock. The QRS duration is slightly prolonged to 0.11 s. The mean manifest frontal plane QRS axis is directed at −60 degrees, reflecting a left axis deviation due to left anterior hemiblock. This results in the following manifestations:

1) There are deep S waves in standard leads II and III and lead aVF. The S wave in standard lead III is 22 mm in depth, i.e. greater than 2 mV.
2) There is a tall R wave in lead aVL.
3) There is a relatively large initial vector directed inferiorly and to the right at about +120 degrees on the frontal plane. This results in prominent initial R waves in standard leads II and III, and lead aVF, and a prominent initial q wave in lead aVL.

The T wave axis is directed inferiorly and to the right at about +110 degrees on the frontal plane. This results in upright T waves in standard leads II and III, and lead aVF, and inverted T waves in standard lead I and lead aVL.

The left anterior hemiblock also results in a prominent terminal S wave in lead V6.

QRST pattern of atrial extrasystoles

The QRST complex associated with the atrial extrasystoles has the following characteristics:

1) The QRS duration is 0.08 s.
2) The mean manifest frontal plane QRS axis is directed at about −45 degrees.
3) The initial r waves are less prominent in standard leads II and III, and lead aVF, than those of the sinus beats.
4) The initial q wave is less prominent in lead aVL than that of the sinus beats.
5) There is a minimal or absent terminal s wave in lead V6.
6) The initial r wave is more prominent in lead V1 than with the sinus beats.
7) The T wave axis is almost in the sagittal plane resulting in equiphasic or minimal T wave deflections in all the frontal plane leads.

Discussion

The left bundle-branch is a relatively flat band which divides almost immediately after leaving the bundle of His into two major sweeps or radiations: the anterosuperior division and the posteroinferior division (Fig. 2). Activation normally occurs concomitantly through both divisions. Terminal activation through the anterosuperior division is downwards and to the right (illustrated as vector 1 in digram A of Fig. 2). Terminal activation through the posteroinferior division is upward and to the left (illustrated as vector 2 in diagram A of Fig. 2).

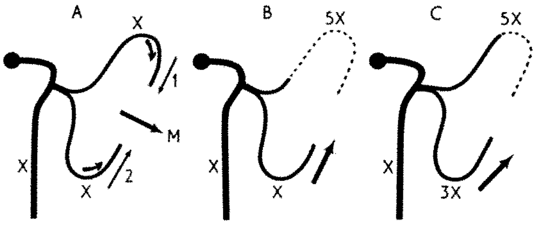

FIG. 2 *Diagrams illustrating the possible mechanism for the paradox of the 'supernormal' phase of hemiblock conduction.*

Since activation occurs concomitantly through both divisions, the two forces complement each other, resulting in a mean vector which is directed downward and to the left (illustrated as vector M in diagram A of Fig. 2). If conduction is delayed or blocked within the anterosuperior division – a left anterior hemiblock – activation will occur solely or dominantly through the posteroinferior division. This results in a vector which is directed upward and to the left – a left axis deviation (diagram B of Fig. 2).

The conduction defects resulting from the hemiblocks have been highlighted by the elegant studies of Rosenbaum and his associates (Rosenbaum, Elizari, and Lazzari, 1968, 1969a, 1970; Rosenbaum *et al.*, 1969b, c, d). They describe four types of left anterior hemiblock.

Type I – standard type – left anterior hemiblock

This is characterized by:

a) A mean frontal plane QRS axis directed between −45 degrees and −60 degrees.
b) There is a normal q wave in standard lead I and lead aVL.
c) The voltage of RI, SII, and SIII is moderate. The S wave in standard lead III has an arbitrary upper limit of 1.5 mV.
d) The left chest leads – V5 and V6 – have relatively deep S waves.
e) The normal initial q waves in the left chest leads tend to disappear.

In the **type II** left anterior hemiblock, the electrocardiographic features of the standard type are modified by a horizontal heart position. In the **type III** left anterior hemiblock, the electrocardiographic features of the standard type are modified by a vertical heart position. These types are not germane to this presentation and will not be considered further here.

Type IV left anterior hemiblock

This is essentially an augmented or more advanced form of left anterior hemiblock. The voltage criteria described in type I are increased. Standard leads II and III have very deep S waves; the S wave in standard lead III exceeds 1.5 mV. This is shown in this case (Fig. 1).

The atrial extrasystoles are associated with the type I or standard type of left anterior hemiblock. The QRS voltage is moderate and much diminished when compared with the sinus beats. The S wave in standard lead III does not exceed 1.5 mV. The initial r waves are still prominent in standard leads II and III, and in lead aVF. The initial q wave is still prominent in lead aVL. The QRS complexes of the atrial extrasystoles tend to vary somewhat depending on the degree of prematurity. Thus, the first extrasystole (third beat) in lead V6 shows the remnant of a much diminished terminal s wave. The second extrasystole (sixth beat) in this lead has no terminal s wave at all. The QRS deviation is only 0.08 s as compared with the 0.11 s of the sinus beats. The T wave axis has deviated to the sagittal plane.

The principal features distinguishing the higher grade of left anterior hemiblock (type IV) from the standard type (type I) are thus clearly evident in this case. They are:

1) An increase in QRS duration.
2) An increase in QRS magnitude, particularly the S waves in standard leads II and III and lead aVF.
3) The development of a terminal S wave in lead V6.

Mechanism of 'supernormality'

It is evident that the atrial extrasystoles which are premature and hence must encounter a greater degree of refractoriness in the conducting tissues are paradoxically conducted with a lesser degree of left anterior hemiblock. It is tempting to apply the term 'supernormal phase' to this paradox, yet consideration of differential refractoriness of the conducting tissues provides a more physiological explanation.

In left anterior hemiblock, conduction is blocked or delayed within the left anterosuperior division, so that the activation pathway travels preferentially through the posteroinferior division, and the territory normally activated by the left anterosuperior division is activated dominantly by the activation front passing through the posteroinferior division.

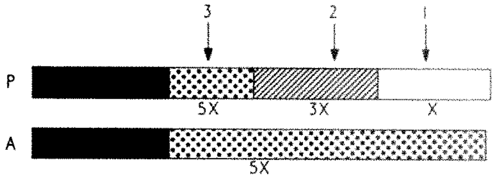

FIG. 3 *Diagram illustrating the possible mechanism for the paradox of the 'supernormal' phase of hemiblock conduction. P = posterior division; A = anterior division; black shading = absolute refractory period; stippled shading = varying degrees of partial refractoriness.*

This would occur, for example, if the anterosuperior division has a much longer conduction time. The principle is depicted in diagram B of Fig. 2 and by impulse 1 of Fig. 3. The posteroinferior division has an arbitrary conduction time of X whereas the anterosuperior division has a much longer conduction time of 5X. Conduction, therefore, occurs solely through the posteroinferior division. An atrial extrasystole, because of its prematurity, encounters a greater state of refractoriness within the posteroinferior division. This is arbitrarily depicted as a conduction time of 3X (diagram C of Fig. 2 and impulse 2 of Fig. 3). This permits a greater synchrony in conduction between the 2 divisions. In other words, there is some conduction through the anterosuperior division and hence a lesser degree of left anterior hemiblock. Theoretically, with even greater prematurity (as depicted diagrammatically by impulse 3 of Fig. 3), conduction time would be equal, and thus occur synchronously through both divisions, and the hemiblock would disappear.

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Inhibition of demand pacemakers caused by potentials associated with inspiration

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A 69-year-old man with a permanent demand pacemaker and a unipolar electrode system had intermittent failure of pacing during deep inspiration. Pacing was not interrupted when the unit was switched to fixed rate mode by an external magnet. Thus, the problem was not caused by a change in electrode position or to a loose connexion. The likely cause was inhibition by non-cardiac potentials, possibly myopotentials associated with respiration.

Since the advent of demand systems in cardiac pacemakers, interference by external electromagnetic field has been well recognized (Furman *et al.*, 1968; Bilitch, Lau, and Cosby, 1967). Recently it has been reported that inhibition can also be provoked by myopotentials emanating from muscles surrounding the pacemaker (Piller and Kennelly, 1974; Gribbin, Abson, and Clarke, 1974; Ohm *et al.*, 1974). The purpose of this paper is to report inhibition of demand pacing caused by muscle potentials associated with deep inspiration in a patient.

Case report

A 69-year-old man presented to the Royal Melbourne Hospital in May 1973, with a history of recurrent syncopal episodes over the preceding 12 months. A demand pacemaker (Telectronic P10) set at a rate of 90/min was implanted with a unipolar endocardial electrode and the patient was followed regularly at the Pacemaker Clinic (Mond *et al.*, 1972). In October 1974, the characteristics of the pacemaker potential showed no change from those recorded 6 months earlier. However, a fault which was detected during one routine test is illustrated in the Fig. The pause following R5 is recorded during deep inspiration, and is terminated by an escape complex. Electronic analysis revealed that tracking potentials were emitted from the pacemaker during the pause: this model of pacemaker is designed to give small non-stimulating pulses synchronous with inhibiting complexes to indicate normal demand function during spontaneous rhythm. The patient remained asymptomatic during these brief periods when pacing was inhibited. The phenomenon was repeatedly observed and recorded during two further visits to the pacemaker clinic and each time this could be easily provoked by deep inspiration. The Fig. (B) shows regular pacing continuing even during deep inspiration after application of the magnet to switch the unit to a fixed rate mode.

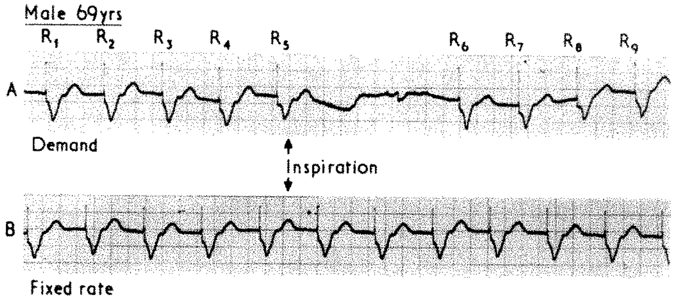

FIG. (*A*) *Demand pacing rhythm, lead II;* (*B*) *Fixed rate pacing rhythm, lead II. Arrows indicate the onset of deep inspiration in both A and B.*

Discussion

Skeletal muscle potentials were first reported to cause inhibition of unipolar demand pacemakers by Wirtzfeld, Lampadius, and Ruprecht in 1972. Such interference has been reported in up to 50 per cent of patients with unipolar pacemakers during either isometric contraction of pectoralis major or arm movements (Wirtzfeld, Lampadius, and Schmuck, 1973; Mymin *et al.*, 1973; Barold, 1974). Similar inhibition by non-cardiac body potentials has not been reported previously in association with deep inspiration. Presumably this phenomenon in our patient was caused by potentials emanating from the respiratory muscles.

The fault was not caused by wire fracture or by a loose connexion, because pacing was maintained during deep inspiration when the system was switched to fixed-rate mode.

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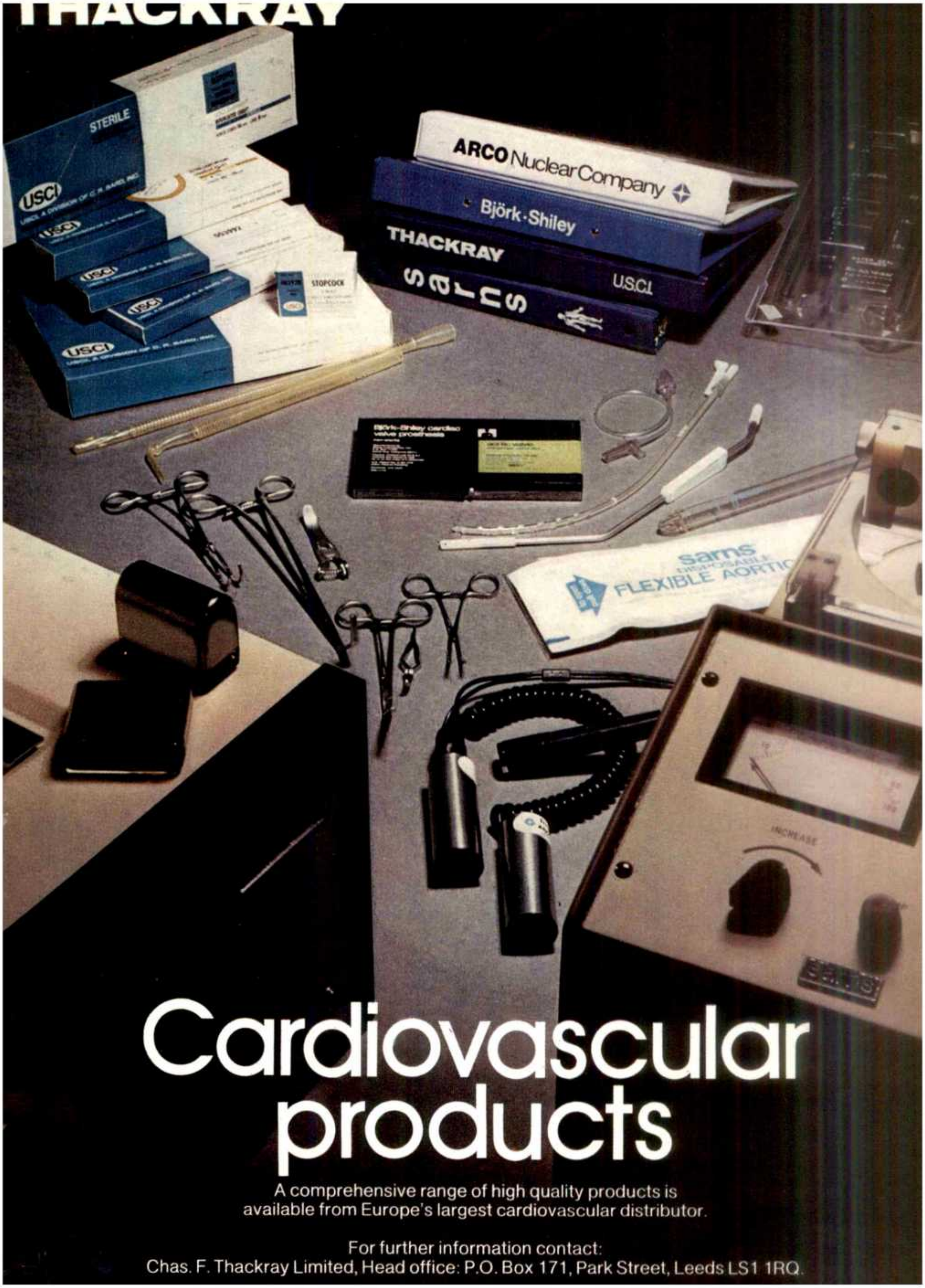

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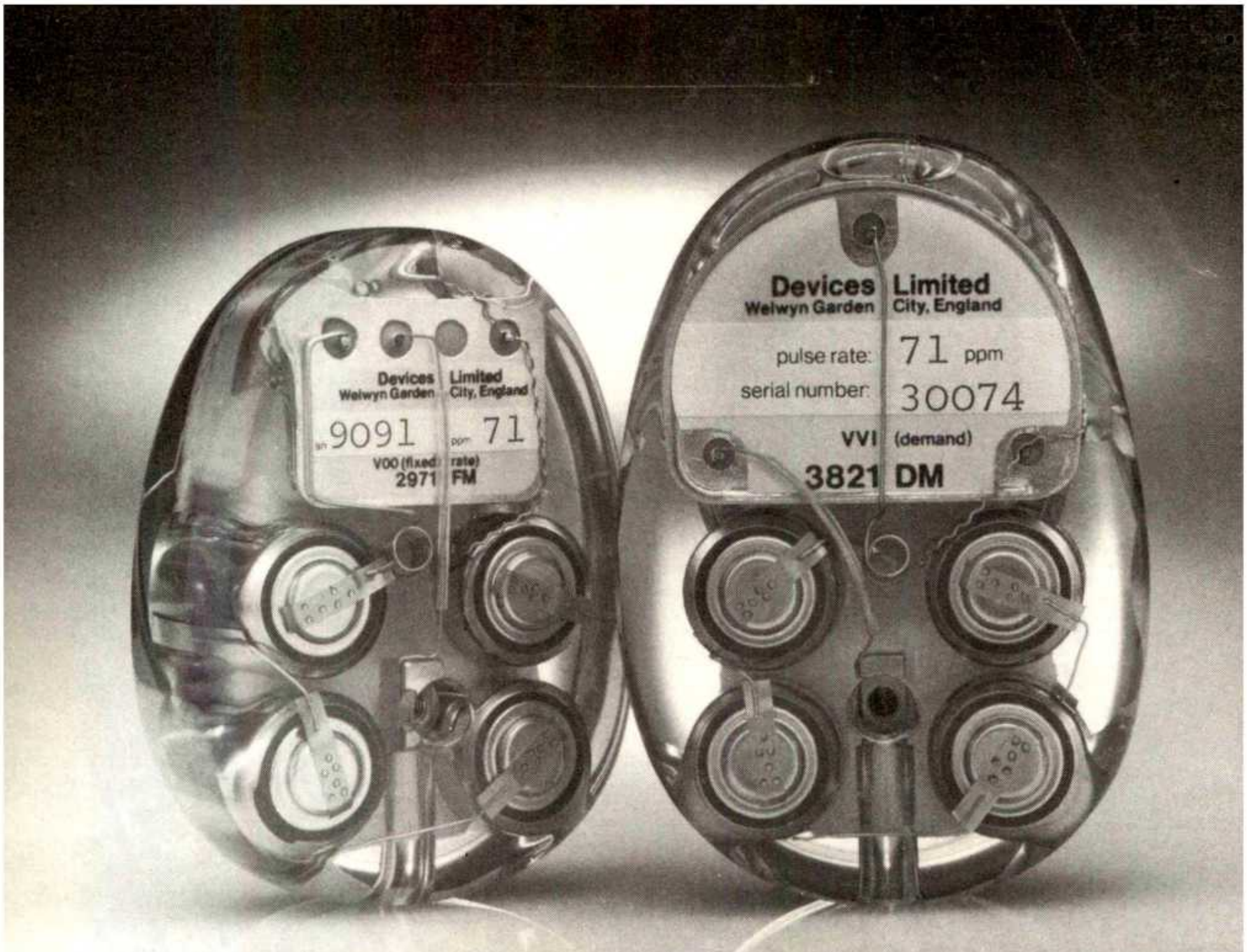

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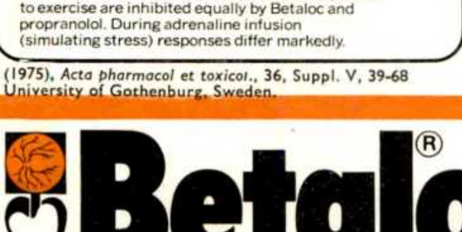

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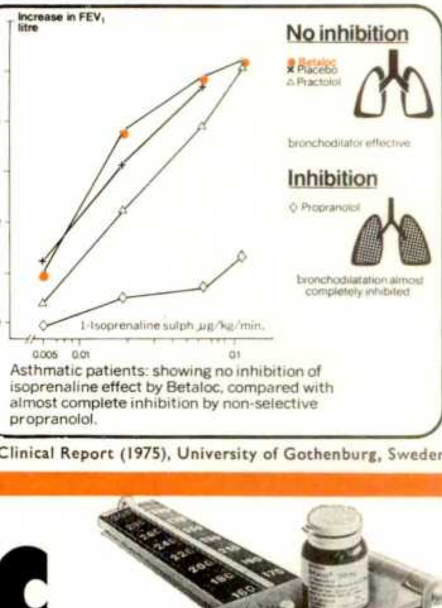

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1 (1975), *Acta pharmacol et toxicol.*, 36, Suppl. V, 39-68 University of Gothenburg, Sweden.

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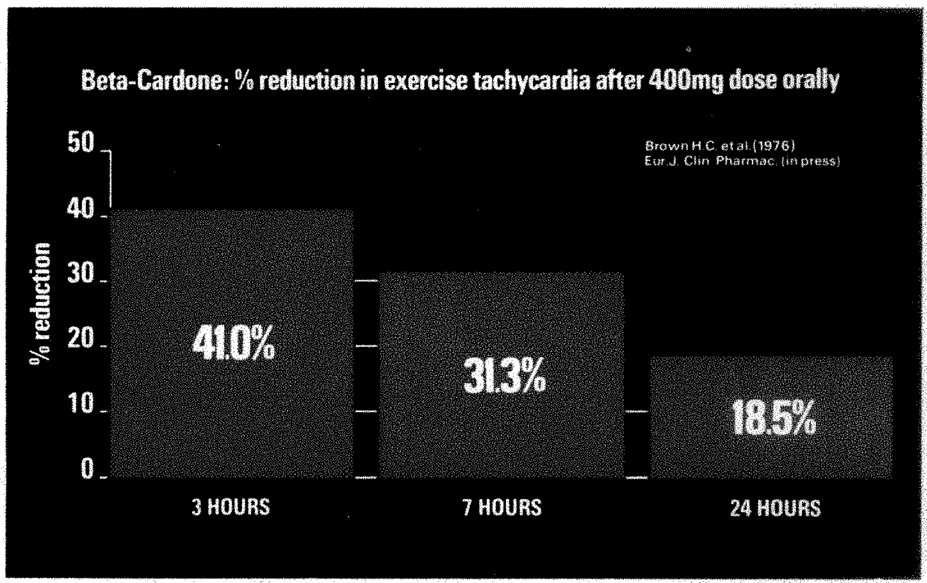

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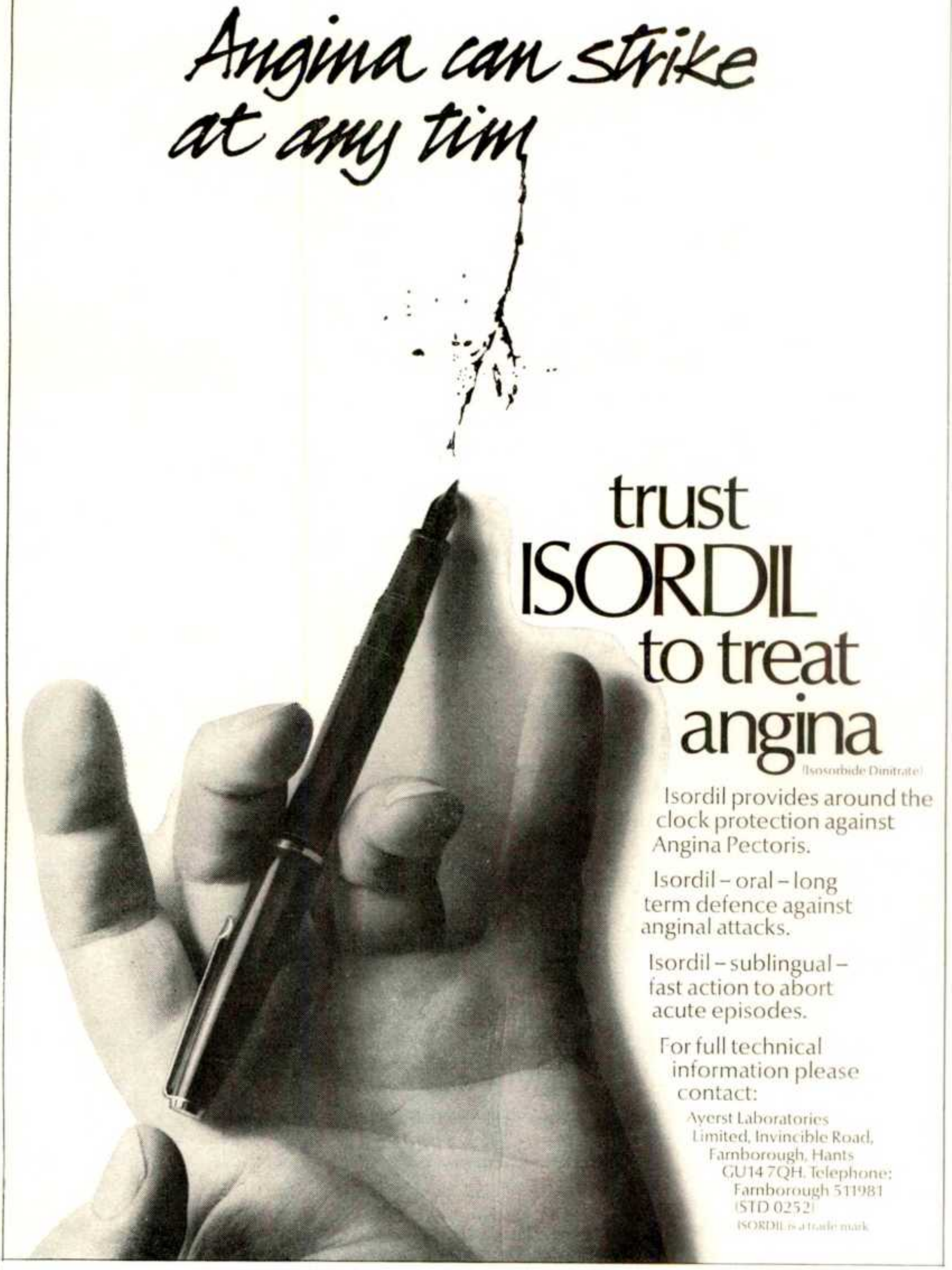

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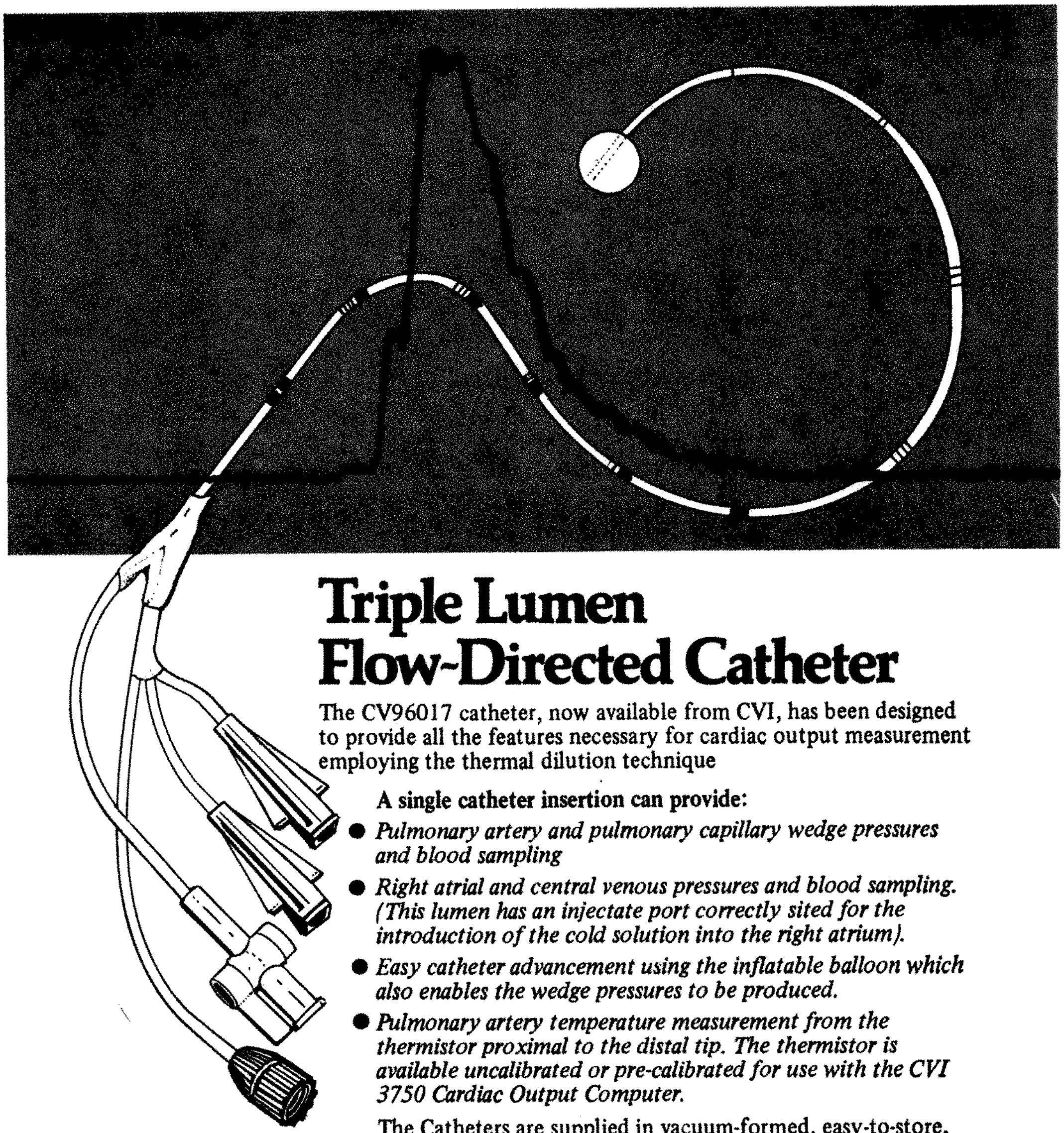

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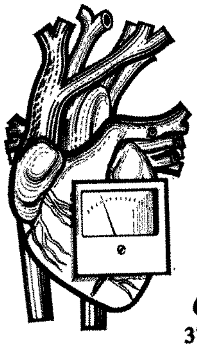

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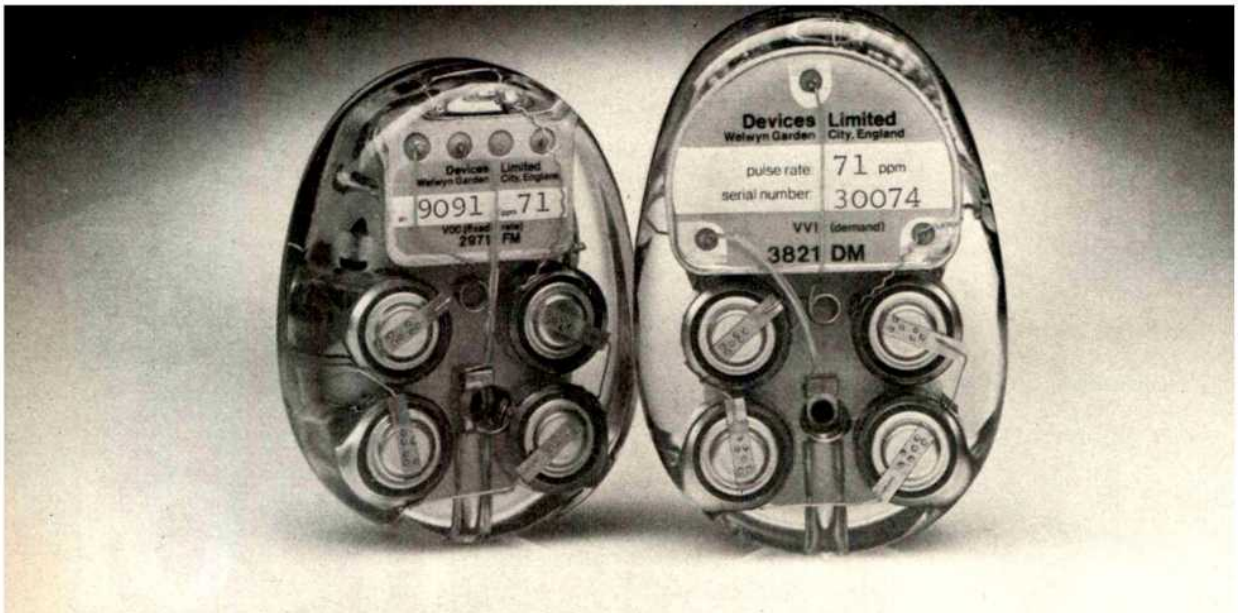

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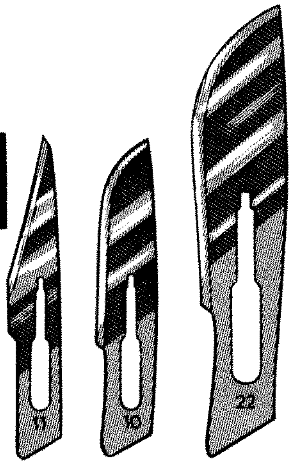

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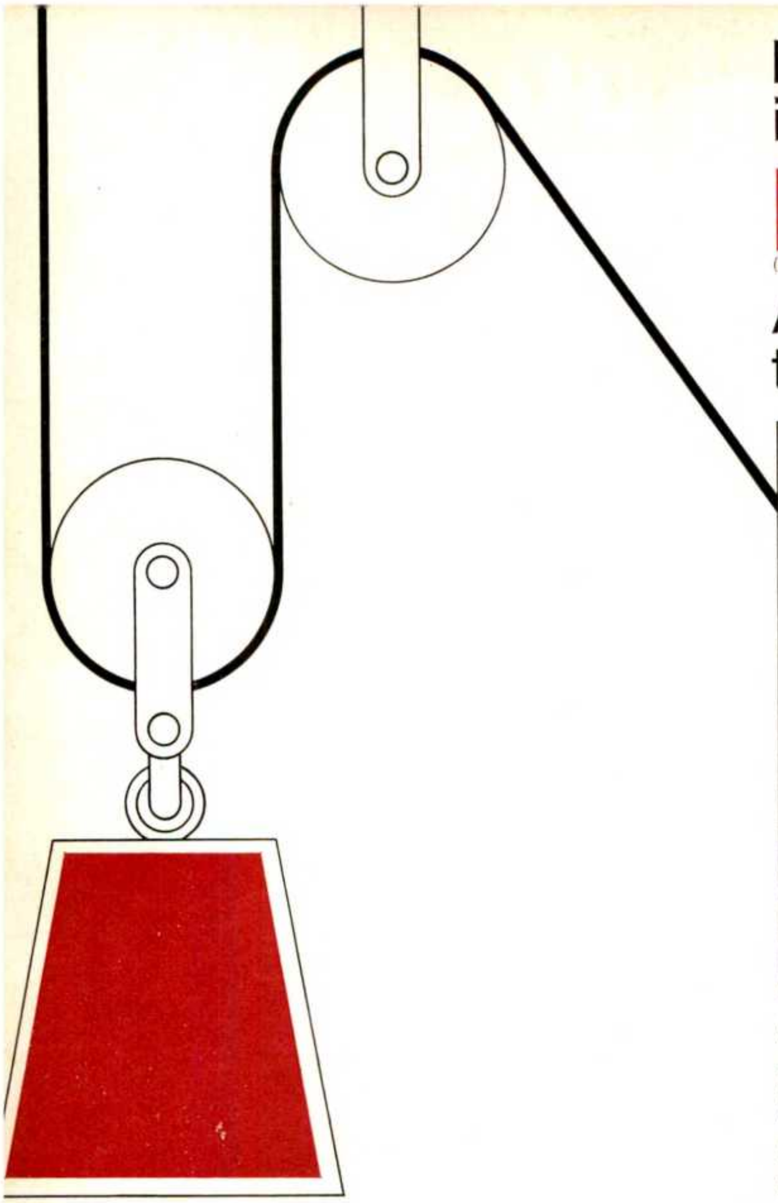

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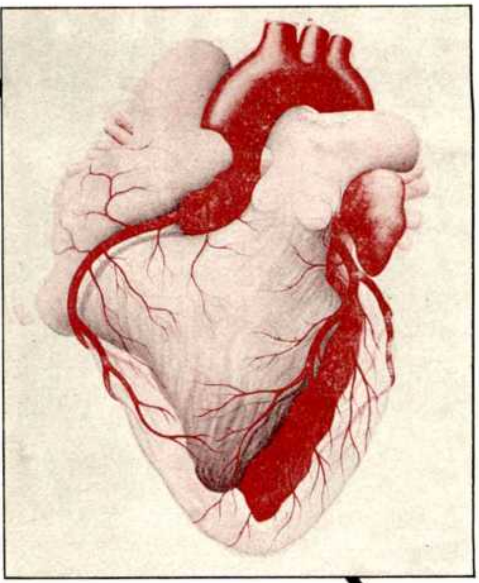

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Editorial

British Heart Journal, 1976, **38**, 213.

The journal and SI units

At first sight it seems that no case can be made for changing from the old to the new SI units of measurement. Practical advantages for the physician are hard to find and indeed no claim has been made that they help or improve on the present situation. Since our editorial introduction to SI units more than a year ago, *British Heart Journal* (1975), **37,** 1), far from any sign of widespread enthusiasm, we have heard them condemned as unnecessary, unsafe, and unwieldy. We know of persons ordinarily silent, being aroused to take pen to paper in protest. The target has been the new system in general, and in particular the change in intravascular pressure measurements. The millimetre of mercury, taken for granted by generations, has become for some an anti-bureaucratic symbol, and a society for its protection has won support from London to Leningrad. It must be noted, however, that when extinction threatened the degree Fahrenheit, pounds per square inch, and the sixpenny bit, the action groups which mushroomed to preserve them soon found the odds too great and now are themselves extinct.

Before last year's decision to accept SI units, we thought hard and long, took counsel from the young and the mature, and weighed up pros and cons. Rereading our earliest ventures in complete conversion to SI units, we found the transition to be fairly easy in most of the biochemical measurements and in body weight. However, blood pressure in kilopascals was almost incomprehensible and the conversion factor at the foot of a table did little to help (e.g. Dolder, M. A., and Oliver, M. F. (1975) 'Myocardial infarction in young men. Study of risk factors in nine countries'. *British Heart Journal,* **37,** 493). We sensed we were not alone in judging the change in the case of blood pressure units to be too abrupt. Our policy for the foreseeable future will be to show systemic blood pressure and intracardiac pressures in millimetres of mercury and venous and cerebrospinal fluid measurements in centimetres of water, with the corresponding kilopascals in brackets. SI units alone will be used for all other measurements.

In the present issue, we reproduce by courtesy of the authors an article 'The use of SI units in cardiovascular studies' by C. T. Kappagoda and R. J. Linden which appears in the current issue of *Cardiovascular Research.* We commend this to all intending contributors and expect them to use it as a guide in preparing their manuscripts. Within the next year, the SI terms will sound less strange and we will find it easier to understand why new entrants to medical schools throughout the country who have been taught only in SI units, ask at the end of the lecture 'What do you mean by milligrams percent and millimetres of mercury?'.

Editorial

British Heart Journal, 1976, **38**, 214-218.

Dietary cholesterol, plasma cholesterol and coronary heart disease

Michael Oliver[1]

Many who study cardiovascular epidemiology, nutrition, or cardiology have neither the will, the wish, nor the time to examine the fabric of the case for or against causal relationships. Opinions are set and deaf ears are turned. The polarization of views in the United States, for example, goes so far as to result in major court actions, alienation between doctors, disagreements within families, excessive advertising, and missionary zeal. Sometimes the advocates of a significant relation between, for example, dietary fat and coronary heart disease speak so loudly and so often that they endanger their own good case by appearing to be uncritical and to overlook inconvenient facts. Exactly the same is true of those who choose to disregard the links between dietary fat and coronary heart disease. I shall try to take the heat out of certain arguments by reappraising some of the facts, though anyone with the temerity to write on this subject is likely, at best, to be labelled injudicious. I shall focus on the relation between dietary cholesterol and coronary heart disease. But first dietary fat must be mentioned briefly.

Dietary fat

Some people equate the total amount of fat in the diet directly with mortality from coronary heart disease. Others consider that there is a definite, proved relation either between the saturated fat content or amount of cholesterol in the diet and a risk of developing coronary heart disease (Fig. 1). Several epidemiological studies indicate a positive correlation between the intake of saturated fat with the incidence of coronary heart disease. The most notable of these are the Seven Countries Study (Keys, 1970), the multiracial community survey in Cape Town (Bronte Stewart, Keys, and Brock, 1955), and studies of immigrants from poor to rich areas, where they were abruptly exposed to a higher standard of living than they had had previously (Toor *et al.*, 1957; Larsen, 1957).

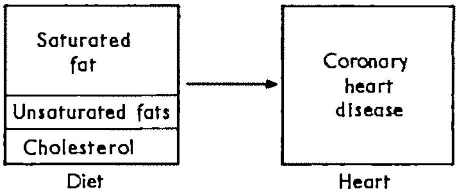

FIG. 1 *A superficial view.*

Most of the evidence has been derived from contrasts between comparatively primitive and rich communities, and there is no convincing evidence that there is a significant correlation between the intake of dietary saturated fat with mortality from coronary heart disease within so-called developed communities, where fat already comprises more than about 35 per cent of total calories. Moreover, it is not solely dietary saturated fat that is important: some have shown that the association is statistically stronger when animal protein is considered (Yerushalmy and Hilleboe, 1957) and when dietary sucrose is taken into account (Yudkin, 1957). These comments should not be interpreted as approbation for the high intake of saturated fat in the UK. There is little doubt that it is one of several important contributory influences on mortality, and as such the arguments set out in the recent COMA Report (1974) for a reduction of dietary saturated fat are surely correct.

Dietary cholesterol

The evidence incriminating dietary cholesterol as a cause of coronary heart disease in developed countries is virtually non-existent. Keys (1970) failed to show a significant relation from less well-developed to affluent countries for this dietary constituent.

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Diets that are high in saturated fat are generally speaking, high in cholesterol. The ordinary mixed diet in the UK contains only between 10·5 and 15·5 mmol (400 and 600 mg) cholesterol daily and the chief source is the egg, which contains 230 mg cholesterol. Other common sources are milk, liver, shellfish, and meat. About 40 to 60 per cent of the cholesterol present in the food is absorbed, so that in very approximate terms 6 mmol (250 mg) cholesterol enters the total body pool from dietary sources each day. Dietary cholesterol of this order has no measurable effect on plasma cholesterol. Extremes of cholesterol intake—excess (Connell, 1959) or none (Kempner, 1948)—do alter plasma levels but even these may have only a transient effect before a new homeostatic balance (see below) is achieved. With higher intakes the percentage of absorption falls and so a daily intake of about 78 mmol (3 g) can lead to the acquisition of no more than 26 mmol (1 g) per day. Probably the amount of cholesterol absorbed is affected by other constituents in the diet, particularly dietary fibre, by the form in which cholesterol is presented, and perhaps by genetic influences on absorption.

Dietary cholesterol is a contributant to plasma cholesterol, though not a major one, and that is about all that can be said about its relation to coronary heart disease.

Plasma cholesterol

The cholesterol circulating in the plasma represents about 10 per cent of the total body pool of cholesterol. There are only very weak correlations between total exchangeable body cholesterol and plasma cholesterol (Goodman and Noble, 1968). There are probably two large pools of tissue cholesterol with very low turnover rates which are independent of the rapidly exchangeable plasma pool (Samuel and Lieberman, 1973). The plasma level of cholesterol is determined by *a*) the amounts synthesized in the body, *b*) the rate of catabolism and excretion in the bile, *c*) the equilibration between plasma and tissues, and *d*) by the amount absorbed from the diet (Fig. 2). These are placed in order of probable importance.

Cholesterol synthesis and the enterohepatic circulation of bile acids form a vital homeostatic mechanism which influences critically the size of the cholesterol pool in the plasma as well as in the body. Bile acids are excreted into the duodenum, modified either by deconjugation or by other chemical changes through the action of bacteria, and some are reabsorbed unchanged in the ileum and returned in the blood to the liver. The rate of bile acid formation increases if the return to the liver is decreased and vice versa. This homeostatic nature of the enterohepatic circulation is very important in adjusting the body's reaction to variations in exogenous cholesterol intake and quite probably acts in a 'protective' role.

If these considerations are not enough to cause confusion in the interpretation of plasma cholesterol concentrations they are compounded by the fact that cholesterol is carried by a number of different lipoprotein fractions (World Health Organization, 1970). The availability and structure of various low density lipoproteins (Scanu, 1973)—and of the apoprotein associated with the binding of cholesterol—also determine the amount of cholesterol carried in the plasma, the duration of its transport, and its availability for catabolism or transfer to tissue; and the presence of high density lipoproteins may be important in relation to removal of cholesterol from tissue (Miller and Miller, 1975).

Genetic factors also influence plasma cholesterol concentrations. Plasma cholesterol levels show greater concordance in monozygotic twins compared with dizygotic twins (Pikkarainen, Takkunen,

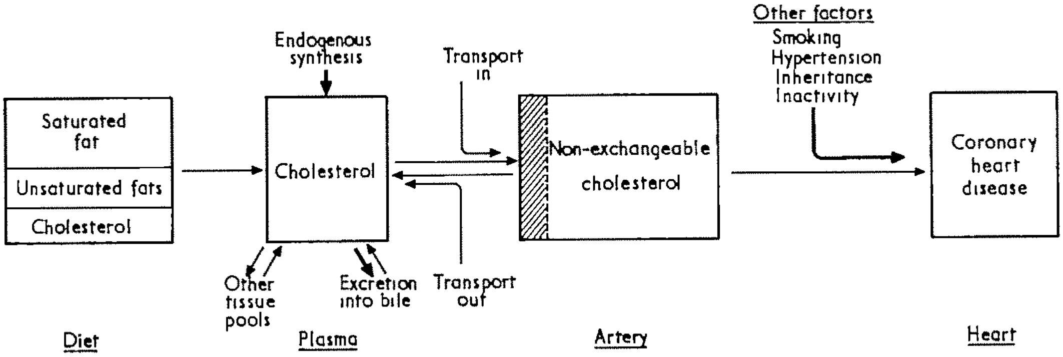

FIG. 2 *Illustration of some other factors which should be taken into account when relating dietary cholesterol to coronary heart disease.*

and Kulonen, 1966). The inheritance of plasma cholesterol concentrations is greater from mother to child than from father to child and all first degree relationships show far greater similarity in plasma cholesterol than that between husband and wife (Schaefer, Adlersberg, and Steinberg, 1958).

The brief account—illustrated partly in Fig. 2—of the controlling influences of plasma cholesterol should emphasize the extreme weakness of relating dietary cholesterol to any pathological process, let alone the clinical features such as coronary heart disease that are one stage removed from that process. The naiveté of placing much clinical and prognostic significance on particular levels of plasma cholesterol—unless very high indeed—in relation to the health of a given individual is also exposed.

Arterial cholesterol

Those who emphasize the importance of plasma cholesterol levels in man do so almost entirely on the positive epidemiological correlation with the incidence of coronary heart disease. The use of a derived end-point—namely, coronary heart disease or other ischaemic manifestations—and not atherosclerosis itself leads to confusion. It may be true that a moderate rise in plasma cholesterol levels in the region of 150 to 250 mg/100 ml, which occurs in most people in developed countries, is contributory to the almost universal presence of coronary atherosclerosis in middle-aged men in these countries, but there is no good evidence that such a rise *by itself* causes the clinical manifestations of angina, myocardial infarction, or sudden cardiac death.

The metabolism of the arterial wall (see Schettler and Weizel, 1974) is the critical intermediary. We do not know the quantitative relation between plasma and arterial cholesterol, and the process of cholesterol accumulation in the arterial wall is complex and not just dependent on concentration gradients. Low density lipoproteins pass directly into the aortic intima (Smith and Slater, 1973) and many factors influence their deposition (Walton, 1975). But the proportion of cholesterol-rich low-density lipoproteins in the plasma is only one side of the equation determining the extent of cholesterol deposition. Some will be catabolized and some will pass through to the veins and lymphatics of the adventitia. The arterial wall is probably protected from accumulation of cholesterol by active transport systems taking cholesterol out of arteries. For example, lecithin cholesterol acyltransferase (LCAT) is responsible for esterification of free cholesterol (Glomset and Norum, 1973) in the arterial wall. The activity of this enzyme is dependent on the availability of high density lipoproteins. Thus the plasma concentration of this lipoprotein may be critically important in determining the amount of cholesterol that can be removed from the arterial wall and ultimately excreted into bile acids.

It is surprising the extent to which other factors important in the genesis of coronary atherosclerosis are still ignored. The effects of increased intravascular pressure are well established, particularly experimentally, and in general the greater the increase the greater the deposition of cholesterol in the arterial wall (Smith and Slater, 1972). The role of fibrin-platelet thrombus formation is undoubtedly contributory to atherosclerosis, though still requiring clearer definition.

The most impressive evidence that pronounced hypercholesterolaemia is associated with an unusually high incidence of atherosclerotic vascular disease lies in the high incidence of this disease, and at a premature age, in individuals with the single gene-determined familial hypercholesterolaemia. The premature onset of coronary heart disease in those thought to be homozygous for this abnormality supports the view that disturbed cholesterol metabolism on a genetic basis plays a significant role. But there are plenty of reported cases of individuals heterozygous for familial hypercholesterolaemia surviving into middle or even late age, with a distinct rise in plasma cholesterol levels. Obviously there are other contributory factors important in determining the onset of coronary heart disease in these people but the contribution of familial hypercholesterolaemia to the total incidence of coronary heart disease is probably small. From the number of coronary deaths in the general population and the frequency with which heterozygotes for familial type IIA might occur, it has been calculated that the coronary death rate for men under 55 years attributable to the familial type II disorder is only 1:400—a surprisingly small contribution to the vast population problem (Slack, 1972).

Additional evidence often adduced to support the relation between high plasma cholesterol levels and atherosclerosis is that a rise in plasma cholesterol levels in animals may lead to arterial lesions, particularly aortic but also coronary in site. Many of these lesions are at best termed 'cholesterolosis' since they often lack, unless very gross, a major collagen response and also any element of platelet-fibrin deposition. Regression studies in several species show that the removal of cholesterol previously added to an experimental diet is associated with a reduction in their lesions. Recent studies in monkeys are more impressive (Armstrong, Warner, and Connor, 1970), though again highly artificial diets were used to induce lesions. That cholesterol-rich lesions can be induced by giving a diet abnormally high in cholesterol, and that these lesions can regress when this diet is removed, is a fact in itself and should be left as such. The contribution of dietary cholesterol to the normal mixed human diet is a fraction of what was given to these animals: the plasma cholesterol levels in man are a fraction of the levels produced in these animals: and the conditions do not mimic the exposure of man to slight rises of plasma cholesterol over many years. As yet the extrapolation of this information to man is unjustified.

It should be clear by now that we are getting further and further away from any direct relation between dietary cholesterol and coronary heart disease. Not only does the plasma have its own intrinsic controlling mechanisms which determine the amount of cholesterol present, but arterial metabolism itself determines the amount of cholesterol stored.

Coronary heart disease

The view that raised plasma cholesterol concentration is *per se* a cause of coronary heart disease is untenable. Cigarette smoking, hypertension, physical inactivity, inheritance, softness of drinking water, and other factors determine the step linking coronary atherosclerosis to coronary heart disease. The importance of these influences has been overshadowed by the cholesterol-coronary heart disease hypothesis, and it is interesting to reconsider the relative degrees of risk of some of these, as appraised in the Framingham data and presented in the Report of the Inter-Society Commission for Heart Disease Resources (1970). The increase in risk for mortality from coronary heart disease for Americans with a diastolic blood pressure higher than 105 mmHg (14·0 kPa) is 2·2 times, for those smoking 20 cigarettes a day it is 1·9 times and for those with a serum cholesterol >7·8 mmol (>300 mg/ml) it is 1·75 times. Those with the aggregated risk for excess cigarette smoking, raised diastolic blood pressure, and hypercholesterolaemia are 8·5 times more likely to have a major coronary event over a 10-year period compared with those not at risk but, even in these individuals, the incidence is only 1·7 per cent per year.

Looking at it another way, 83 per cent of such high-risk people are alive 10 years after identification. Perspective is helped when it is realized that about 1 in 12 of that population had serum cholesterol levels above 7·8 mmol/l (300 mg/100 ml), and only 1 in 25 of these men died from coronary heart disease between the ages of 45 and 54 years. Applying these figures to the population in the United Kingdom it can be deduced that only 1 in 7 of the coronary deaths occurring at this age is associated with pronounced hypercholesterolaemia even though coronary deaths represent about 35 per cent of the total number of deaths.

Conclusion

Dietary cholesterol is not an important cause of coronary heart disease, and a moderate regular intake is not harmful.

But the high intake of saturated fat in developed countries is one of several factors contributing to coronary heart disease and, therefore, represents a health hazard. It is good sense, therefore, for healthy individuals to reduce the total amount of saturated fat and also the total calorie intake, which is often excessive.

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British Heart Journal, 1976, **38**, 219–224.

The use of SI units in cardiovascular studies[1]

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The International System of units (SI) in its present form was adopted as a primary system of measurement by the General Conference of Weights and Measures (CGPM) in 1971 and it represents the most recent phase in the evolution of a rational system for the quantification of scientific data. It has its roots in the metric system and has already been adopted as the only legally acceptable system of measurement in nearly thirty countries. In essence, the system accepts only one unit for any one physical quantity. Thus, seven base units (see later) are used for the measurement of length, mass, time, electric current, thermodynamic temperature, luminous intensity, and the amount of substance. Any other unit used in science and technology can be derived from these base units without the incorporation of arbitrary numerical factors.

These aspects of the problems are illustrated in the derivation of an SI unit of force which is expressed as *mass* x *acceleration*. The basic SI units for mass, length, and time are the kilogram, the metre, and the second, respectively. Thus velocity will be expressed as metre per second and acceleration (which is the rate of change of velocity) as metre per second per second. Therefore, the SI unit of force will be that force which, when applied to a mass of *one* kilogram, will produce in *one* second an increase in velocity of *one* metre per second. This force is called the newton. Thus the only numerical factor involved in the derivation of this unit is unity: and larger or smaller forces can be expressed by prefixes representing 10 raised to multiples of the power 3. These procedures eliminate the use of somewhat arbitrary multiples and submultiples in the conventional British system, e.g. 16 ounces = 1 pound; 746 watts = 1 horse power.

Summary of SI units

The International System of Units recognizes three classes of units:

(i) Base units
(ii) Supplementary units
(iii) Derived units.

(i) Base units

The International System is founded on seven base units listed below in Table 1.

TABLE 1

Quantity	*Name of base unit*	*Symbol*
Length	metre	m
Mass	kilogram	kg
Time	second	s
Electric current	ampere	A
Thermodynamic temperature	kelvin	K
Luminous intensity	candela	cd
Amount of substance	mole	mol

(ii) Supplementary units

Supplementary units are those units which have not yet been classified either into base units or derived units and are shown in Table 2.

TABLE 2

Quantity	*Name of supplementary unit*	*Symbol*
Plane angle	radian	rad
Solid angle	steradian	sr

(iii) Derived units

This third category includes all other units used in scientific work and includes two main subgroups.

(a) This subgroup includes derived units which are denoted by names having their origin in proper names. These units in addition to being expressed in terms of base or supplementary SI units (Table 3A) will also have special names and symbols.
(b) Derived units which are expressed algebraically

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[1] This paper is being published simultaneously in *Cardiovascular Research*.

in terms of the base (or supplementary) units and the symbols for such units incorporate the mathematical symbols for multiplication or division, e.g. the SI unit for velocity is metre per second (m/s) (Table 3B). For convenience, certain units which are derived from units listed in Table 3A above have also been included in that category, e.g. stress is denoted by newton per square metre ($N{\cdot}m^{-2}$).

It is clearly not practical to compile a complete list of derived units, but a list of units commonly employed in cardiovascular studies is shown in Table 3. Readers are referred to the British Standards Institution publication number PD5685 (1972) for a more comprehensive list of these units.

TABLE 3

A. *Named derived units*

Quantity	*Name of derived unit*	*Symbol*	*Expression in terms of base units*
Frequency	hertz	Hz	$1\ Hz = 1/s$
Force	newton	N	$1\ N = 1\ kg \cdot m/s^2$
Pressure	pascal	Pa	$1\ Pa = 1\ N \cdot m^{-2}$
Work, energy, quantity of heat	joule	J	$1\ J = 1\ N \cdot m$
Power	watt	W	$1\ W = 1\ J/s$
Quantity of electricity	coulomb	C	$1\ C = 1\ A \cdot s$
Electrical potential, potential difference, electromotive force	volt	V	$1\ V = W \cdot A^{-1}$
Electric capacitance	farad	F	$1\ F = 1\ A \cdot s\ V^{-1}$
Electric resistance	ohm	Ω	$1\ \Omega = 1\ V \cdot A^{-1}$
Electric conductance	siemens	S	$1\ A = 1\Omega^{-1}$

B. *Other derived units*

Quantity	*SI units*	*Symbol or definition*
Area	square metre	m^2
*Volume	cubic metre	m^3
†Density	kilogram per cubic metre	$kg\ m^{-3}$
Velocity	metre per second	m/s
Acceleration	metre per second per second	m/s^2
Kinematic viscosity	square metre per second	m^2/s
Dynamic viscosity	pascal second	$Pa \cdot s$
‡Specific heat	joule per kilogram kelvin	$J \cdot kg^{-1} \cdot K^{-1}$
‡Thermal conductivity	watt per metre kelvin	$W \cdot m^{-1} \cdot K^{-1}$
Molality	mole per kilogram	$mol \cdot kg^{-1}$
Concentration	mole per cubic decimetre	$mol\ dm^{-3}$
Stress	newton per square metre	$N \cdot m^{-2}$

*The CGPM has accepted the litre (1) as an alternative name for the $(dm)^3$ and this unit is recommended as a unit of volume for common usage.

†The CGPM has recognized kg per litre as a derived unit of density because it is of practical value.

‡When the Celsius scale of temperature is used for measurement, it is convenient to substitute degree Celsius (°C) for kelvin (K) in this derived unit, since an interval of one degree Celsius is equal to one kelvin.

Notes on the use of SI units

Use of multiples

In order to avoid excessively large or small numerical values in quantifying commonly used information (e.g. arterial blood pressure), the CGPM has recommended the use of multiples and submultiples of the SI units (e.g. 100 mmHg = 13·3 kPa). These factors are denoted on the prefixes and symbols shown in Table 4.

TABLE 4

Factor by which the unit is multiplied	*Name of prefix*	*Symbol of prefix*
10^{12}	tera	T
10^{9}	giga	G
10^{6}	mega	M
*10^{3}	kilo	k
10^{2}	hecto	h
10	deca	da
10^{-1}	deci	d
10^{-2}	centi	c
10^{-3}	milli	m
10^{-6}	micro	u
10^{-9}	nano	n
10^{-12}	pico	p
10^{-15}	femto	f
10^{-18}	atto	a

*In the case of the SI unit for mass, it should be noted that the prefix is appended to the gram which is not the base unit.

When using these prefixes, particular attention should be paid to the following points:

(i) When a prefix is applied to a unit, it becomes a part of that unit to constitute a new unit which can then be subject to any applied power, e.g. $1\ mm^3 = 1\ (10^{-3}m)^3 = 10^{-9}m^3$ and is *not* equal to $10^{-3}\ (m^3)$.

(ii) Only one prefix should be applied to a unit at any one time, e.g. one thousandth of a millimetre is not a milli milli metre (mmm) but is a micro metre (μm).

(iii) Errors in calculation could be avoided if quantities are expressed as powers of 10 instead of prefixes.

(iv) The prefixes should be attached to the numerator of compound derived units whenever it is practicable.

(v) When selecting a multiple for expressing a quantity it should be such that the numerical value lies between 0.1 and 1000, e.g. 0.000 2 m can be written as 0.2 mm; 1500 Pa = 1.5

kPa (see note on the measurement of blood pressure).

(vi) The use of prefixes representing 10 raised to a power which is a multiple of ± 3 is recommended. The prefixes hecto (10^2), deca (10^1), deci (10^{-1}) and centi (10^{-2}) should be limited so far as possible to uses when the recommended prefixes are inconvenient.

(vii) The decimal sign between digits is indicated by a full stop. No commas are used to divide numbers with five or more significant figures into groups of three, but instead the digits are separated by spaces into groups of three starting from the decimal sign. When there are only four figures a space is not needed. If the numerical value is less than unity a zero should precede the decimal sign, e.g. 1001; 0.000 001; 23 000.

Use of symbols denoting SI units

In the interest of consistency, the following rules should be observed in using these symbols.

(i) The symbols should be written in roman (upright) type regardless of the type used in the text.

(ii) They should be unaltered in the plural.

(iii) They have no final full stop to denote abbreviations.

(iv) They should be written after the complete numerical value in the quantity leaving a space between the quantity and the unit. If a prefix is used there should be no space between it and the symbol, e.g. 2.54 kPa; 3.85 mm etc.

(v) The unit symbol should be in the lower case except in those symbols which are derived from proper names, e.g. Pa, A, K, etc.

(vi) Multiplication in a compound unit is denoted by a mid point (i.e. a 'raised full stop'), e.g. the moment of a force about a point is measured by multiplying the force by the perpendicular distance between the point and the force. Thus, moment = force × distance. The SI unit of moment is the newton metre and the symbol for it is written N·m.

(vii) When a compound unit is formed by *dividing* a unit by another, the negative index should be used except where the *divisor* is a unit of time when the solidus (/) should be used. Thus concentrations will be expressed as mol· litre^{-1} and blood flow will be expressed as litre/min.

Special units

There are certain units which have been retained by the CGPM because of their practical importance. Of particular interest in cardiovascular studies are the following:

Quantity	*Name of unit*	*Unit symbol*	*Definition*
*Time	minute	min	
	hour	h	
	day	d	
†Volume	litre	l	1 litre = 1 dm^3

*The international symbol for year is 'a' (annum) but should be written in full as 'year'.

†To avoid ambiguity between 1 and l, litre should be written in full when such ambiguity could arise.

SI units which have particular relevance to cardiovascular studies

(i) Volume The SI unit of volume is the cubic metre (m^3) which is inordinately large for most clinical and experimental situations. Therefore, the International Committee on Weights and Measures have recommended the retention of the litre (l) which is identical to the cubic decimetre (dm)^3. The litre is, therefore, a special name for the cubic decimetre and will be used. For smaller volumes, the cm^3 and mm^3 should be used.

(ii) Concentrations The SI accepts two methods of expressing concentration, both of which use the litre as the unit of volume. In the case of those materials whose molecular weight is known (e.g. plasma electrolytes, urea, drugs, etc.) multiples and submultiples of the molar concentration expressed as mol· litre^{-1} should be used. This procedure will eliminate the usage of the equivalent concentrations which are not SI units.

In instances when the molecular weight is not known with any certainty (e.g. plasma proteins, haemoglobin, active component of vitamin B_{12}), the mass concentration should be used and expressed in terms of the litre, e.g. g· litre^{-1}, mg· litre^{-1}. However, in the case of haemoglobin the concentration should be expressed as g· dl^{-1} (where 1 dl = 100 ml).

Finally, in quantifying the formed elements of blood, it has been conventional to express the values in terms of a cubic millimetre, e.g. white blood cell count = 6000 mm^{-3}. These values should be expressed in terms of a litre. The use of the litre as the unit of volume would increase the actual count by 10^6 but would leave the significant figures unaltered. Thus a white blood cell count of 6000 mm^{-3} would be 6. 0 · 10^9 litre^{-1} in SI units.

(iii) Measurement of cardiac output Although the base unit of time is the second the cardiac output should continue to be reported in terms of litre/min.

The practice of expressing cardiac output in terms of the body surface area merits a closer scrutiny. The errors involved in estimating body surface in adults have been well publicized (Krovetz, 1965). These errors are amplified in newborn infants in whom the measurement of length which is used in the calculation is notoriously difficult. Thus, cardiac output should be expressed in terms of body weight which at least has the virtue of being measured to a known accuracy.

(iv) Pressure, peripheral resistance, and work To physiologists interested in the cardiovascular system the intravascular pressures are of particular importance. In themselves, they provide primary information and the derivatives of pressure such as stroke work, dP/dt max, vascular resistance, etc. provide much valuable information about the state of the myocardium and the peripheral circulation.

Pressure In the past pressures have been expressed in terms of either mmHg or cm H_2O. Derivatives of pressures such as stroke work or vascular resistance have been expressed either in arbitrary units incorporating mmHg or in terms of dynes. The SI unit for force is the newton, and accordingly the unit of pressure is the newton per square metre which is known as the pascal. The SI units for work and power are the joule and the watt, respectively. The derivations of these units are summarized in Table 3A. It is beyond the scope of this article to provide details of the relation between the conventional units of pressure and the pascal but suffice it to state that 1 mmHg= 133.332 Pa and 1 cm H_2O=98.0665 Pa. Thus if the kilopascal (1 mmHg=0.133 kPa) is employed as the unit of pressure, arterial systolic pressure of 130 mmHg will be equal to 17.3 kPa and a mean atrial pressure of 10 cm H_2O will be 0.98 kPa. It is felt that to avoid confusion the same multiple of the pascal, the kPa, should be retained for all intravascular pressures and also to convey the magnitude of the difference between pressure in the low and in the high pressure systems of the circulation.

Peripheral resistance It is conventional to calculate peripheral resistance from the formula:

$$\text{Resistance} = \frac{\text{Pressure difference}}{\text{Flow}}$$

The units adopted for this value are either arbitrary (peripheral resistance unit) or calculated in dyne· s· cm^{-4}. Before formulating yet another unit, it is necessary to consider briefly the value of resistance denoted in this way. Vascular resistance is widely used as a measure of vessel bore, and many investigators tend to use it as a means of defining changes in vessel diameter after the administration of drugs, e.g. β-adrenoreceptor antagonists.

This approach to the problem is conceptually erroneous as the relation between pressure and flow is non-linear and hence changes in calculated resistance as indicated by changes in a value derived by dividing 'pressure' by 'flow' could occur without changes in vessel diameter. However, changes in vessel diameter may be calculated, from pressure/flow curves or, by measuring changes in pressure at a constant flow. Though this discussion is an over-simplification of the problem of investigating changes in vessel bore, it is sufficient to indicate some of the difficulties which may be experienced in this field and to point to the need for the use of a single unit of measurement.

Because of these considerations it seems inappropriate for general purposes, such as the examination of changes in vessel bore, to formulate a specific unit based on SI. Instead it is recommended that peripheral resistance be expressed as follows:

$$\text{Resistance} = \frac{\text{Pressure difference (kPa)}}{\text{Flow (litre/min)}}$$

e.g. for a pressure gradient of 13.0 kPa (97.8 mmHg) and a blood flow of 5 litres/min the vascular resistance would be 13.0/5=2·6 kPa· litre^{-1}· min. When expressed in this way (i.e. with absolute values of pressure and flow presented) the readers will not be left in any doubt if a change in flow has occurred and will, therefore, be in a position to judge the validity of any interpretation placed on the calculated values of resistance. For those specialized investigations dealing with resistance as a physical phenomenon and not using it particularly as an index of vessel bore it would be acceptable to express resistance in recognized SI units. Thus the unit of resistance would be Pa· m^{-3}· s.

Stroke work Stroke work is calculated as follows: Stroke work=Stroke volume × (Mean arterial pressure − left ventricular end-diastolic pressure).

The SI unit of work is the joule (J) which is the amount of work done by a force of one newton in moving an object a distance of one metre. Thus, to express stroke work in joules it is necessary to express stroke volume in cubic metre (m^3) and the arterial pressures in newton per square metre (i.e. pascal). Stroke work for a stroke volume of 70 cm^3 and a mean arterial pressure of 13.0 kPa (97.8 mmHg) would be calculated as follows:

Stroke volume $= 70\ \mathrm{cm}^3 = 70 \times 10^{-6}\mathrm{m}^3$
Mean arterial pressure $= 97{\cdot}8\ \mathrm{mmHg} = 13{\cdot}0\ \mathrm{kPa} = 13{\cdot}0 \times 10^3\ \mathrm{Pa}$
Thus stroke work $= 70 \times 10^{-6} \times 13{\cdot}0 \times 10^3$ joule·beat^{-1}
$= 910 \times 10^{-3}$ joule·beat^{-1}
$= 0{\cdot}910$ joule·beat^{-1}

Bicycle ergometry Bicycle ergometres are usually calibrated in kilopond metres/min (kpm/min) which are not SI units. The appropriate unit is the watt and the relation between it and the kilopond metre/min is derived as follows:

1 kpm/min $= [1$ kg (i.e. force) $\times 9{\cdot}8\ \mathrm{m/s}^2$ (i.e. acceleration due to gravity)$] \times [1$ m (i.e. distance)$]$
$= [9{\cdot}8\ \mathrm{kg \cdot m \cdot s^{-2}}] \times 1$ m per min
$= 9{\cdot}8$ newton $\times 1$ m per min
$= 9{\cdot}8$ joule per min
$= 9{\cdot}8/60$ watt
$= 0{\cdot}163$ W.

Thus, a value for load in a representative exercise test on a patient with heart disease would be 25 W (153 kpm/min).

(v) Viscosity

In a Newtonian liquid the coefficient of viscosity

$$= \frac{\text{Force}}{\text{Area} \times \text{Velocity gradient}}$$

The commonest unit of viscosity is the poise which is derived from the c.g.s. system.

$$1\ \text{Poise} = \frac{1\ \text{dyne}}{[\text{cm}]^2 \times \left[\dfrac{\text{cm}}{\text{s}} \times \dfrac{1}{\text{cm}}\right]}$$

$$= \frac{1\ \text{dyne}}{\dfrac{\text{cm}^2}{\text{s}}}$$

$$= \frac{1\ \text{dyne} \times \text{s}}{\text{cm}^2}$$

In SI the units of force, area, and velocity gradient are the newton, m² and $\frac{1}{s}$ respectively. Thus the conversion is effected as follows:

$$1\ \text{Poise} = \frac{\left[\dfrac{1}{1000}\ \text{kg} \times \dfrac{1}{100}\ \text{m/s}^2\right] \times \text{s}}{\left[\dfrac{\text{m}^2}{10\,000}\right]}$$

$$= \frac{\left[\dfrac{1}{100\,000}\ \text{kg}\cdot\ \text{m/s}^2\right] \times \text{s}}{\left[\dfrac{\text{m}^2}{10\,000}\right]}$$

$$= \frac{\left[\dfrac{1}{100\,000}\ \text{N}\right] \times \text{s}}{[\text{m}^2/10\,000]} = \frac{1}{100\,000} \times \frac{10\,000}{1}\ \frac{\text{N.s}}{\text{m}^2}$$

$$= 0.1\ \text{Pa·S}$$

1 centipoise = 0·001 Pa· s, i.e. 1mPa· s
Therefore the viscosity of blood would be approximately 2·55 mPa· s.

(vi) Temperature The SI unit of temperature is the kelvin which is applicable for thermodynamic temperature and for expressing differences in temperature. However, the degree Celsius (°C) which is identical to the original 1 degree centigrade has been accepted as suitable for denoting temperature for ordinary purposes. The temperature interval for a °C is the same as one kelvin. The relation between the two systems is expressed by the following. The Celsius temperature $t = T$ (thermodynamic) $-T_0$ where $T_0 = 273.15$K.

(vii) Blood gases and acid-base data Standard atmospheric pressure will continue to be used as an international reference. It is defined as 101.325 kPa. The conventional reference condition of standard temperature and pressure (STP) will then be 0° Celsius and 101.325 kPa.

The partial pressure of gases used for calibrating blood-gas instruments should, therefore, be denoted in kPa instead of mmHg. The CO_2 and O_2 tensions should also be expressed as such. This step may well be limited by the enthusiasm of the manufacturers to modify the scales of the instruments.

With respect to *p*H, there is clearly no SI unit for it. The only way in which this could be achieved is by converting the *p*H value to H^+ concentration and then expressing this value in terms of mole of H^+ per litre. The arguments for and against this have continued for nearly two decades and a solution does not appear to be in sight, but suffice it to add that such a step would give a spurious impression that the H^+ concentration can in fact be measured and tends to endow the measurement with an aura of precision it does not possess. The units of *p*H will remain the same.

The non-respiratory acid-base disturbances are usually quantified in terms of standard bicarbonate, base deficit and excess which are expressed as milli-equivalents. In SI units the appropriate unit will be the millimole. Since the bicarbonate ion is monovalent, there will be no change in the numerical value. However, it must be remembered that standard bicarbonate itself is conceptually incorrect when used to analyse acid-base disturbance *in vivo* and could lead to inaccurate diagnoses. The authors recommend that the use of the terms standard bicarbonate, base deficit and excess be discontinued (Stoker *et al.* (1975) for references). Such a change is, at the moment, arguable and, therefore, would not be mandatory in articles in this journal.

The aspects of SI which are of particular interest to those engaged in cardiovascular studies have been reviewed in this article, bearing in mind the necessity for formulating a concise and consistent editorial policy regarding units. As a consequence, much of the element of choice permitted by the CGPM regarding abbreviations and symbols has been eliminated from these recommendations. The reader is, however, referred to two other documents listed in the references for more detailed information.

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Appendix 1

Definitions of the SI base-units

Metre
The metre is the length equal to 1 650 763.73 wave lengths in vacuum of the radiation corresponding to the transition between the levels $2p_{10}$ and $5d_5$ of the krypton-86 atom.

Kilogram
The kilogram is the unit of mass; it is equal to the mass of the international prototype of the kilogram.

Second
The second is the duration of 9 192 631 770 periods of the radiation corresponding to the transition between the two hyperfine levels of the ground state of the caesium –133 atom.

Ampere
The ampere is that constant current which, if maintained in two straight parallel conductors of infinite length, of negligible circular cross-section, and placed 1 metre apart in vacuum, would produce between these conductors a force equal to 2×10^{-7} newton per metre of length.

Kelvin
The kelvin, unit of thermodynamic temperature, is the fraction 1/273.16 of the thermodynamic temperature of the triple point of water.

Candela
The candela is the luminous intensity, in the perpendicular direction, of a surface of 1/600 000 square metre of a black body at the temperature of freezing platinum under a pressure of 101 325 newtons per square metre.

Mole
The mole is the amount of substance of a system which contains as many elementary entities as there are atoms in 0 012 kilogram of carbon 12.

Appendix 2

Commonly used terms in cardiovascular studies

Force	newton (N)
Flow	litre/min
Blood flow through specific organ	litre/min· kg^{-1} tissue
Cardiac output	litre/min· kg^{-1}
Heart rate	beats/min
Oxygen consumption	cm^3/min or litre/min
Potential difference	volt (V)
Power	watt (W)
Pressure	kilopascal (kPa)
Partial pressure of gases	kPa
Rate of change of pressure	dP/dt (kPa/s). The maximum rate of change of pressure should be denoted by dP/dt max
Resistance—vascular (see text)	kPa· $litre^{-1}$· min
Temperature	degree Celsius (°C)
Time	second (s)
	minute (min)
	hour (h)
	day (d)
Viscosity	pascal second (Pa· s)
Volume	litre (to be written in full except when used with a prefix)
Work	joule (J)

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Creatine kinase MB isoenzyme studies in diagnosis of myocardial infarction

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Serial measurements of the MB isoenzyme of creatine kinase, total creatine kinase, aspartate aminotransferase, and urea stable lactate dehydrogenase have been made in the serum of a series of 139 patients admitted with a diagnosis of suspected myocardial infarction. Serum MB isoenzyme measurements have also been made on postoperative surgical patients and patients with medical disorders known to have caused raised serum total creatine kinase activity.

All these enzymes were abnormal in at least one specimen from all patients with electrocardiographically proved acute myocardial infarction. The magnitude of the MB isoenzyme rise was 2 to 3 times greater than that of any of the other enzymes. The duration of its rise was relatively short. The MB isoenzyme was more specific for myocardial infarction than other enzymes and no increases were found in postoperative patients, except in those after cardiac bypass surgery. The MB isoenzyme seems the most sensitive and specific test for myocardial infarction available, though there are technical problems in its accurate measurement.

The 3 routine enzyme tests most commonly used for the diagnosis of myocardial infarction—namely, aspartate aminotransferase (AST, also known as GOT), lactate dehydrogenase (LD), and creatine kinase (CK)—are not specific for the myocardium: higher concentrations of each of these enzymes may be present in other tissues.

Creatine kinase has 3 principal isoenzymes which are dimers which may contain type B or type M polypeptide chains (Dawson, Eppenberger, and Kaplan, 1965). The BB isoenzyme is found in brain, the MM isoenzyme is the principal component in both skeletal muscle and the myocardium, while the MB isoenzyme is found as a minor component (about 30% of the total CK) in the myocardium and is present in only very small amounts in most skeletal muscles. The MB isoenzyme is, therefore, relatively heart-specific. Though this was reported some time ago (van der Veen and Willebrands, 1966), it is only more recently that a number of investigators have suggested that measurement of serum MB isoenzyme activity may be the most sensitive and specific test for myocardial infarction currently available (Konttinen and Somer, 1972; Roe *et al.*, 1972; Smith, 1972).

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We report here serial studies of the MB isoenzyme of CK in the sera of 139 patients with suspected acute myocardial infarction, of patients with raised total CK activity from causes other than myocardial infarction, and in normal ambulant men.

Patients

Patients with suspected acute myocardial infarction

These comprised 142 patients admitted to the Coronary Care Unit, The Royal Infirmary, Edinburgh, with a diagnosis of suspected myocardial infarction. The load of specimens would have been too great if all consecutive admissions had been included in the study, so allocation to the trial group was on a random, blind basis on arrival at the unit. The patients were classified into the following groups according to electrocardiographic and clinical findings. The enzyme results were not taken into account in making this classification.

1) *Myocardial infarction*—68 patients whose electrocardiograms fulfilled the criteria for 'very probable' myocardial infarction (World Health Organization, 1959)—that is, they showed pathological Q waves, raised ST segment, and subsequent T wave inversion.

2) *Possible myocardial infarction*—14 patients whose electrocardiograms showed fewer diagnostic abnormalities ('possible' myocardial infarction, World Health Organization, 1959), usually ST segment or T wave

changes, or had coexistent or previous changes which precluded inclusion in (1).

3) *'Coronary insufficiency'*—42 patients who had typical cardiac pain unaccompanied by anything more than transient changes in the electrocardiogram.

4) *'Non-infarction'*—15 patients in whom a diagnosis of ischaemic heart disease was thought to be unlikely.

The 139 patients in these groups comprised 109 men and 30 women; 3 further patients were excluded from the study as they died before sufficient data were obtained. Full details of any trauma or excessive exercise before admission were obtained from each patient. Intramuscular injections and resuscitation procedures were also specifically recorded.

Patients without myocardial infarction but with disorders giving rise to raised serum CK activity

These comprised 221 patients. Of these 221 patients, 36 had undergone cardiac bypass operations, mostly for valve replacement, 170 had undergone a variety of non-cardiac surgical operations varying from cystoscopy to major abdominal surgery; 9 were on haemodialysis for acute renal failure; 4 were in grades 3 or 4 coma as a result of barbiturate overdosage; and 2 were 'miscellaneous' patients, one with hypothermia the other with Munchausen syndrome.

Control group

This comprised 132 apparently healthy men, blood donors aged between 30 and 60 years, from whom reference values for the serum enzyme assays were obtained.

Methods

Samples were obtained on admission from patients admitted to the coronary care unit and thereafter at about 6, 12, 18, 24, 36, 48, and 72 hours after admission. Serum was separated within 2 hours of sample collection. Most enzyme analyses were made on the day the sample was received; all others were made within 3 days after storage at +4°C. All specimens with visible haemolysis were rejected.

The following methods were used for serum enzyme activity measurements.

Creatine kinase: Rosalki (1967), using reagents supplied by the Boehringer Corporation, London. Between-batch precision (±1 SD) in the range up to 300 IU/l was 6 IU/l.

Aspartate and alanine aminotransferase: A modification (Smith, Brown, and Taylor, 1970) of the method of Henry *et al.* (1960). Between-batch precision in the range up to 50 IU/l was 1·8 and 2·1 IU/l, respectively, for AST and alanine aminotransferase (ALT).

Urea stable lactate dehydrogenase: Brydon and Smith (1973). Between-batch precision in the range up to 500 IU/l was 20 IU/l.

Rate measurements for the above kinetic methods were made at 37°C at 340 nm using an LKB 8600 reaction rate analyser.

Creatine kinase isoenzymes: These were quantified after separation and staining on polyacrylamide gel slabs (Smith, 1972). Sample volume was 10 μl, serum was diluted if necessary in 40 per cent sucrose to give an activity of 200 IU/l. The stained bands of creatine kinase activity were quantified after densitometry with a Vitatron TLD 100 Flying Spot densitometer by integrating the area under the MM and MB isoenzyme peaks. It was possible to obtain reproducible results only when the MB isoenzyme activity exceeded 10 IU/l, since staining of the isoenzymes was too faint when activity was less than this figure.

The precision of the MB isoenzyme determination was calculated from the results of between-batch repeat analysis of patients' specimens. This indicated an overall coefficient of variation of 15 per cent. The accuracy of the quantification procedure was checked by mixing known proportions of human myocardial MM and MB isoenzymes of CK which had been partially purified by anion exchange chromatography: these mixtures were then analysed by the electrophoretic technique. The results (Fig. 1) indicate that the method is accurate for values below 40 per cent MB isoenzyme within the limits of precision of the technique.

Results

Reference values ('normal range')

The distribution of results for all serum enzymes from the control group was log-normal. The corresponding reference values (Table 1) are 90 per cent confidence limits (5th to 95th centiles) obtained by the relevant graphical parametric methods. From our own previous studies as well as those already published (e.g., Goldberg and Winfield,

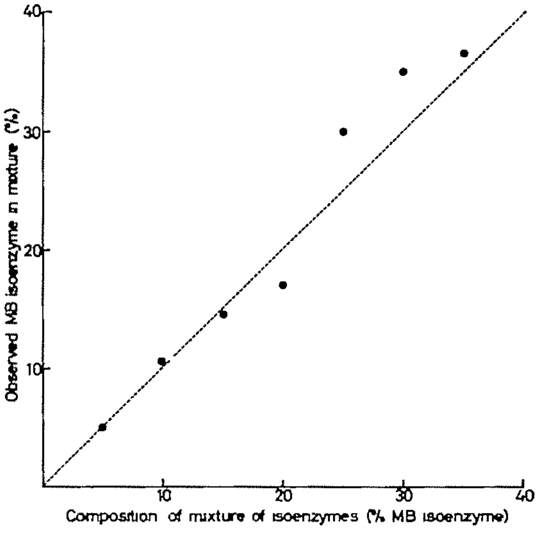

FIG. 1 *Mixtures of known composition of MM and MB isoenzymes of creatine kinase were analysed by electrophoresis and quantified on polyacrylamide gel slabs.*

TABLE 1 *Reference values: healthy ambulant men aged 30 to 60 years*

	Enzyme activity (IU/l)			
	No.	*Mean*	*SD*	*Reference range*
Creatine kinase	131	102*	45*	40–200*
Creatine kinase MB isoenzyme	131	Not detectable		0–10
Aspartate aminotransferase	99	20·2	4·9	10–30
Urea stable lactate dehydrogenase	98	203	49	100–300
Alanine aminotransferase	99	19·2	7·8	10–35

*These figures do not include a result of 2460 IU/l.

1974) the following upper reference limits for women were assumed: AST and ALT 25 IU/l, CK 150 IU/l.

The reference values for the MB isoenzyme require further comment. The limit of sensitivity of the present technique was 10 IU/l; below this though MB isoenzyme bands might be visible, they could not be precisely quantified. Therefore samples in which the MB isoenzyme could not be detected, as was the case with all our normal healthy controls, were reported as less than 10 IU/l. A number of independent reports (Yasmineh and Hanson, 1975; Nealon and Henderson, 1975; Henry, Roberts, and Sobel, 1975) have suggested reference ranges of between 0 and 4 IU/l and 0 to 7 IU/l. Probably, therefore, the lower limit of detection by our method—that is, 10 IU/l—is fairly close to the upper reference value for normal men. We therefore accepted this value in this study, though probably the figure is a little high.

Patients with myocardial infarction

In most of these patients (53/68) the initial blood specimen was obtained within 6 hours of the onset of chest pain, and in the remainder specimens were obtained within 24 hours. The activity of each of the serum enzymes was raised in at least one specimen in all 68 patients in this group. The serum levels of the MB isoenzyme differed from the other enzymes in two major respects.

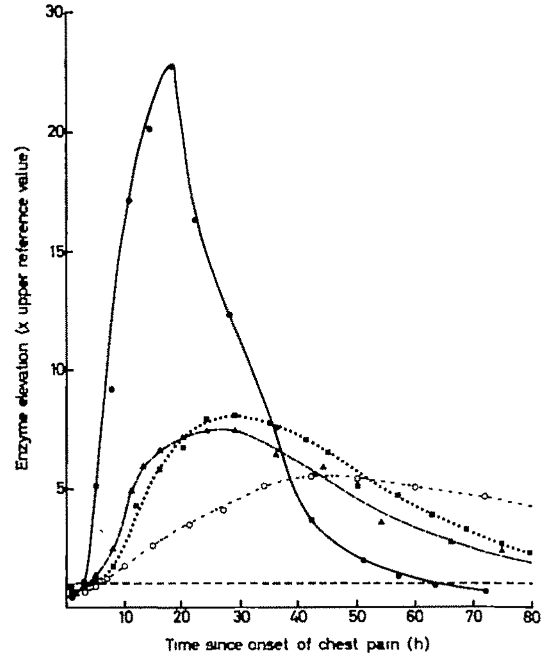

FIG. 2 *Mean serum enzyme activities in group 1 patients at varying intervals after myocardial infarction.* ●——●, *MB isoenzyme;* ▲— — —▲, *creatine kinase;* ■......■, *aspartate aminotransferase;* ○......○, *urea stable lactate dehydrogenase.*

1) The MB isoenzyme activity rose to higher levels (relative to the upper reference value) than any of the other enzymes (Table 2). For each enzyme the 'peak activity' was the highest measured enzyme activity. With 6-hourly sampling the actual peak may have been missed for the MB isoenzyme in some cases, since the serum levels changed rapidly; much flatter peaks were obtained for the other enzymes.

2) The MB isoenzyme became abnormal earlier, reached its peak activity earlier, and returned to normal earlier than the other enzymes (Table 3, Fig. 2).

The proportion of the total CK contributed by

TABLE 2 *Maximum serum enzyme results in patients with myocardial infarction*

	Upper reference value (IU/l)	*Serum enzyme activity (× upper reference value)*		*Time of peak activity (h since onset of pain)*	
		Mean	*Range*	*Mean*	*Range*
Creatine kinase	200	8·6	1·5–16	23	9–48
MB isoenzyme	10	22·2	2·8–70	18	8–30
Aspartate aminotransferase	30	8·3	1·3–20	26	11–48
Urea stable lactate dehydrogenase	300	5·7	1·2–14	40	11–69

TABLE 3 *Incidence of abnormal serum enzyme activities at varying intervals since onset of symptoms of myocardial infarction*

Interval since infarction (h)	*No. of specimens*	*CK (MB)*	*% abnormal results* CK	*AST*	*Urea stable LD*
0–6	51	58	28	32	18
7–12	56	98	93	95	78
13–18	53	100	98	98	96
19–24	55	96	94	94	96
25–36	54	94	97	97	98
37–48	50	66	98	98	100
48–72	55	41	85	95	100

CK (MB), MB isoenzyme of creatine kinase; CK, Creatine kinase; AST, Aspartate aminotransferase; LD, Lactate dehydrogenase.

the MB isoenzyme was very variable, both in specimens showing peak MB isoenzyme activity and those showing peak total CK activity. This percentage MB isoenzyme at the MB isoenzyme peak was not related to the magnitude of CK increase (Table 4), to the site of the infarct, to any history of angina or previous myocardial infarcts, or to the age or sex of the patient.

The plasma half-life of the MB isoenzyme was calculated in those patients in whom adequate data were available. Data obtained after enzyme levels had begun to fall were used, on the assumption that by this time significant release of enzyme from the myocardium had ceased. The MB isoenzyme had a mean plasma half-life of 7 hours (range 4 to 12 hours) compared with 18 hours for total CK and 24 hours for AST.

The patient who showed the least pronounced rise in MB isoenzyme activity (28 IU/l) had fairly high activity of CK, AST, and urea stable LD (921, 124, and 1248, IU/l, respectively). It was a feature of these enzyme changes, however, that the enzyme activities remained relatively static throughout the period of 72 hours while the patient remained in the coronary care unit rather than showing the usual peak followed by a decline. This suggests that the patient may have had a series of small extensions to his infarct, causing a much larger rise in CK, AST, and urea-stable LD than in the MB isoenzyme because of the much shorter plasma half-life of the latter.

TABLE 4 *Variability of MB isoenzyme percentage at MB isoenzyme peak*

% MB isoenzyme at MB isoenzyme peak	*No. of patients*	*Mean total CK at MB isoenzyme peak (IU/l)*
Not detectable	0	—
0–4	1	—
5–9	12	1020
10–14	9	1080
15–19	17	940
20–24	13	827
25–29	6	1051
30+	10	1024

Patients with probable myocardial infarction
While electrocardiographic changes were less developed in the 14 patients in this group, most were sufficient, when reviewed with the clinical findings, to warrant a diagnosis of recent intramural infarction. Twelve patients had characteristically raised CK, MB isoenzyme, AST, and urea stable LD results which followed the typical myocardial infarction pattern, and there seems no doubt that this diagnosis was correct in these patients.

A further two patients showed a rise only in the MB isoenzyme; the other enzymes showed small rises within the reference range. One of these patients developed unequivocal electrocardiographic and enzyme evidence of infarction 4 days later; the other also developed highly suggestive sequential electrocardiographic changes.

Patients diagnosed as having myocardial ischaemia
There were 42 patients in this group. Ten of them showed enzyme changes characteristic of myocardial infarction with a rise in all cardiac enzymes. The electrocardiographic findings in these 10 patients were variable: 1 was normal, 5 showed evidence of previous infarction but no fresh changes other than transient ST segment rise, 6 showed transient ST segment changes, 2 had arrhythmias, and 1 showed digitalis effects; more than 1 of these abnormalities were sometimes present. In 20 patients all enzyme results were normal. In the remaining 12 patients enzyme rises were present, but in the light of clinical and laboratory data these enzyme changes were thought to be the result of factors other than myocardial infarction. Further details are given in Table 5.

TABLE 5 *Abnormal enzyme results in patients with chest pain from causes other than myocardial infarction*

Diagnosis	*Enzyme results (IU/l)* *MB isoenzyme*	*CK*	*AST*	*Urea stable LD*
MB isoenzyme mainly affected				
Paroxysmal atrial fibrillation	45	260	50	420
Pericarditis	40	N	N	N
Unexplained chest pain	28	N	N	N
CK mainly affected				
Unexplained (? myositis)	N	664	68	320
Following dental extraction	N	460	N	N
Unexplained	N	340	N	N
Adams-Stokes attack	N	300	N	350
AST mainly affected				
Unexplained*	N	N	420	N
Heart failure*	N	N	230	340
Alcohol excess*	N	N	100	N
Heart failure*	N	N	90	630
Unexplained*	N	N	69	N
Unexplained*	N	N	46	N
Alcohol excess	N	N	41	N
Urea stable LD mainly affected				
Haemolysis	N	490	80	3700
Heart failure	N	N	34	520
Unexplained	N	N	N	340

*These patients all showed increased serum alanine aminotransferase activity.
N—within the reference range.

Patients diagnosed as having 'non-cardiac' disorders

In 10 of these 15 patients all enzyme results were normal; in the remaining 5 one or more enzyme results was abnormal. These patients are also included in Table 5.

After reviewing all the evidence, 92 of the 139 patients were thought to have had a myocardial infarct. In 90 of these all 'cardiac enzymes' were raised, in 2 only the MB isoenzyme was raised. Seventeen of the 47 patients thought not to have had myocardial infarcts had raised enzyme activities. This important group will be considered in more detail, since such cases most often cause diagnostic difficulty and consequently misdiagnosis.

In only 3 cases was a rise in the MB isoenzyme not attributed to myocardial infarction. Two of these were readily explicable in terms of release from myocardium—patients with paroxysmal tachycardia and pericarditis. The remaining patient, a man of 32 with a history of alcoholism, presented with chest pain which clinically did not seem to be of cardiac type. The MB isoenzyme activity (28 IU/l) was the only abnormal enzyme finding, and the electrocardiogram was normal.

Of the 6 patients with raised serum CK activity not caused by infarction, it was impossible to ascertain the cause with confidence in 3, though 2 of them had had intramuscular injections. However, in these 3 patients and in the patients with rises after dental extraction and an Adams-Stokes attack the MB isoenzyme was absent from serum. Thus, 5 out of 6 patients in this group with raised total CK had normal MB isoenzyme findings—a feature that highlights the value of isoenzyme studies in these anomalous cases.

Aspartate aminotransferase seemed the least specific of the enzyme tests in that 11 patients had increases unrelated to myocardial infarction. Most of these patients probably had hepatocellular damage (2, for example, had been drinking very heavily before admission); in 6 patients the ALT results were valuable, as large increases in this enzyme were also present. Thus, if ALT results are taken into account in interpreting AST findings the overall specificity of AST is probably not much different from CK and urea stable LD.

The urea stable LD results suggest this is a fairly specific test for myocardial damage. However, a number of specimens showing minor degrees of haemolysis had to be rejected. Experience has shown that even such minor degrees of haemolysis, which in a busy routine laboratory may often be missed, can cause significant increases in urea stable LD activity.

Postoperative patients (Table 6)

a) Cardiac bypass Most of these had received valve replacements, with periods on bypass usually of between 2 and 4 hours. All 36 patients had raised

TABLE 6 *MB isoenzyme findings in patients with diagnosis other than myocardial infarction*

Category	*No. of patients*	*No. with raised CK activity*	*Range of CK activities (IU/l)*	*MB isoenzyme in patients with raised CK (IU/l)*			
				<10	*10–49*	*50–99*	*>100*
Cardiac bypass	36	36	240–2300	24	6	5	1
Surgical postoperative	170	46	up to 2500	46	0	0	0
Acute renal failure	9	6	up to 940	6	0	0	0
Self-poisoning	4	3	up to 960	3	0	0	0

CK levels but in only 12 was the MB isoenzyme detectable. In only one case, however, was the MB isoenzyme percentage greater than 10, suggesting that most of the CK in the serum of these patients had arisen from skeletal muscle.

b) Other postoperative patients We have demonstrated only 46 out of 170 patients with raised serum CK after operation, though this figure should not be regarded as necessarily indicating the true incidence of such increases, since a single random specimen was obtained from each patient and therefore serum CK increases which may have been detectable with serial blood sampling would have been missed. No patient showed an MB isoenzyme in his serum.

Other disorders giving rise to raised serum CK activity (Table 6)
None of the patients with acute renal failure or barbiturate overdosage showed any MB isoenzyme activity in their serum. One patient with hypothermia had a serum CK of 5100 IU/l; no MB isoenzyme was present in his serum. Another patient was admitted to the coronary care unit (but not included in the trial) complaining of severe chest pain. His electrocardiogram was abnormal but showed no evidence of recent infarction: however, his serum CK was 3400 IU/l; AST and urea stable LD were normal. No MB isoenzyme was present in his serum. Further inquiries at other hospitals in South Scotland indicated that he had visited several of them before his arrival in Edinburgh, with a similar story in each case. It is not clear why this man with the Munchausen syndrome had such a high serum CK.

Discussion

The merits of any new test must be compared with the known advantages and disadvantages of existing tests. Firstly, clinical considerations should be paramount, though methodological and other factors may affect the final decision whether to put a test into routine diagnostic use.

In many cases enzyme tests have to confirm or refute a diagnosis of myocardial infarction. The information may be required for a decision on immediate management—for example, whether to keep a patient in a coronary care unit—and it may be of importance to long-term management and prognosis. Detailed analysis of enzyme results may also give a good index of infarct size (Sobel *et al.*, 1972). Indeed, creatine kinase results obtained in the first few hours after admission have been used to predict infarct size (Shell *et al.*, 1973). These authors now claim that by using such studies they can assess the efficiency of certain drugs in reducing the size of infarcts (Shell and Sobel, 1974).

If the enzyme findings are taken into account in classifying the patients into 'infarction' and 'non-infarction' groups 92 of our 139 patients probably had infarcts. Though there are differences in the overall sensitivity of serum CK, AST, and urea stable LD they are relatively minor, since in 90 of the 92 cases all 3 enzymes were abnormal. In the remaining 2 cases only the MB isoenzyme was abnormal. Taking this evidence in conjunction with the fact that the average magnitude of MB isoenzyme rise was at least 2 or 3 times as great as that of the other enzymes, there seems little doubt that MB isoenzyme measurements are appreciably more sensitive indices of myocardial damage than enzyme tests hitherto available.

It may be questioned whether quantitative MB isoenzyme assays are necessary, since in the present study the combination of total CK (or AST) and a qualitative assessment of the MB isoenzyme was usually sufficient for the diagnosis of myocardial infarction. There are three main reasons why such measurements could be of use. Firstly, small amounts of myocardial damage could be detected if a more sensitive assay technique could be developed for routine use. Secondly, MB isoenzyme measurements may, by showing a secondary rise, indicate the occurrence of an extension to an existing infarct not detected by the other enzymes because of their slower return to normal levels. Thirdly, because of its inherent specificity for myocardium, MB isoenzyme measurements should be especially valuable in the prediction and measurement of infarct size. We have found, however, that the MB isoenzyme contributes such a variable proportion of total CK (Table 4) that estimates of infarct size based solely on MB isoenzyme assay may be unreliable, at least until the precision of measurement of MB isoenzyme activities approaches that obtainable for other enzymes.

The lack of specificity of enzyme tests is probably of more concern than any lack of sensitivity. In this respect, MB isoenzyme measurement clearly stands out as superior to any other tests both from the results reported here and those obtained elsewhere (Wagner *et al.*, 1973; Konttinen and Somer, 1973). Whereas CK, AST, and urea stable LD may individually lack specificity, if the results from all three assays are considered together perhaps with the addition of ALT the overall specificity of the group is much improved and is likely to be equal to if not better than that of the MB isoenzyme. The MB isoenzyme should not, however, be regarded as truly specific for myocardium. In the present study the MB isoenzyme was raised in the serum of one patient (an alcoholic) who almost certainly had no myocardial disease: one of us has previously described an apparently healthy man with a serum CK of 400 IU/l who had an increased serum MB isoenzyme (Smith, 1972). The isoenzyme may also be raised in the serum of patients with muscular dystrophy (Goto, Nagamine, and Katsuki, 1969).

Although few difficulties are likely to arise with raised serum enzyme activities in renal disease and as a result of barbiturate overdosage, problems in the immediate postoperative period are much more common. In general, AST, CK, and urea stable LD may be expected to be raised after any surgical operation of any magnitude; this invalidates their use of the detection of postoperative myocardial infarction. It seems likely that the MB isoenzyme measurements may be very valuable in these circumstances since non-cardiac surgery is not accompanied by rises in serum levels of the MB isoenzyme.

Probably the major clinical restriction of the value of MB isoenzyme measurement lies in its short duration of rise. Though it becomes raised before other enzymes this is only a matter of an hour or so and probably not of major importance, whereas the fact that in many cases activities have returned to normal within 36 to 48 hours after the onset of pain may sometimes limit its value. On the other hand, this feature does allow detection of reinfarction or extension of an infarct. Presumably the rapid fall in MB isoenzyme activity is merely an expression of its short half life in plasma (about 7 hours).

In contrast to the relatively minor clinical drawbacks to MB isoenzyme usage there are technical difficulties concerned in its accurate quantification. At present ion exchange chromatography or electrophoresis is used most widely. Most methods are tedious or imprecise or both but simplified techniques are now becoming available, sometimes as commercial reagent kits. Our experience with one such kit (Corning Eel electrophoresis system[1]) suggests that reasonably accurate and precise results for MB isoenzyme activity may be obtained within an hour or so of receipt of the specimen.

Our data from the present study suggest that MB isoenzyme measurement is 1) the most sensitive test for myocardial infarction currently available provided blood samples are taken 12 to 30 hours after the onset of pain; 2) the single most specific test for myocardial infarction; and 3) the only test that materially aids the diagnosis of myocardial infarction in patients in whom there are other causes —for example, surgery or trauma—for generalized enzyme release from damaged tissues (Dixon *et al.*, 1973). We think that these are sufficient reasons to justify the more widespread use of MB isoenzyme measurement.

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[1] Corning-Eel, Evans Electroselenium Ltd., Halstead, Essex, England.

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Correlation between praecordial accelerocardiogram and left ventricular pressure

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The praecordial accelerocardiogram possesses important practical advantages over more familiar techniques of recording praecordial pulsations. We have compared the amplitude of the P wave of the praecordial accelerocardiogram in 6 normal subjects (group 1) and 21 patients with heart disease (group 2) at rest and after 3 minutes of isometric handgrip at 30 per cent maximum voluntary contraction.

At rest in group 2 there was a significant linear correlation between the amplitude of the P wave of the accelerocardiogram, relative to the maximum systolic amplitude (P/DE), and the left ventricular end-diastolic pressure ($P < 0{\cdot}01$). However, comparison of the data for P/DE showed that the mean value ($\pm$SEM) of 29 ± 5 per cent in group 1 was not significantly different from the mean value of 37 ± 4 per cent in group 2 ($P > 0{\cdot}30$).

During handgrip the mean amplitude of the P wave did not increase significantly in group 1 ($P > 0{\cdot}20$) but increased significantly in group 2 ($P < 0{\cdot}02$). In group 2 there was a significant linear correlation between the percentage increase in the amplitude of the P wave of the accelerocardiogram during handgrip and the percentage increase in the left ventricular end-diastolic pressure ($P < 0{\cdot}01$).

An abnormal increase in left ventricular filling pressure during a stress test is a sensitive indicator of the presence of heart disease (Amende *et al.*, 1972; Fisher *et al.*, 1973; Grossman *et al.*, 1973; Helfant, DeVilla, and Meister, 1971; Kivowitz *et al.*, 1971; Krayenbuehl *et al.*, 1972; Parker, Di Giorgi, and West, 1966; Quinones *et al.*, 1974; Wiener, Dwyer, and Cox, 1968). It would be valuable if this pathological response could be detected by non-invasive techniques that could be used in screening programmes. Various workers have described the appearance of accentuation of a fourth heart sound on the phonocardiogram (Aronow *et al.*, 1971; Cohn *et al.*, 1973; Siegel *et al.*, 1972) and an increase in the amplitude of the 'a' wave of the apex cardiogram (Benchimol and Dimond, 1962; Dimond and Benchimol, 1963; Ginn *et al.*, 1967; Rios and Massumi, 1965; Siegel *et al.*, 1972) during acutely stressful manoeuvres. However, technically satisfactory apex cardiograms may be difficult to record in some patients, while conventional phonocardiography is not a quantitative technique and its value in this context is therefore somewhat limited.

The praecordial accelerocardiogram, which measures the instantaneous acceleration of praecordial movement throughout the cardiac cycle, bears a close similarity in its configuration to the low frequency phonocardiogram (Luisada, 1962) and has been used for this purpose in children (Bew *et al.*, 1971). It differs from the phonocardiogram in that it has a linear response from DC to 25 Hz. It also has the important practical advantage of being relatively insensitive to respiratory movements (Luisada, 1962; Reuben and Littler, 1973; Rosa and Kaplan, 1960). Furthermore, the positioning of the transducer and patient is not as critical as with the apex cardiogram (Reuben and Littler, 1973). Measurement of the amplitude of the systolic waves of the praecordial accelerocardiogram has previously been shown to provide valuable information about left ventricular systolic performance (Hume, Irving, and Reuben, 1974; Reuben and Littler, 1973). We were therefore interested to see if we could detect changes in the diastolic properties of the left ventricle by this simple, non-invasive technique.

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Subjects and methods

Our subjects comprised 6 healthy, normal volunteer members of the staff (group 1) and 21 patients with heart disease (group 2), 8 of whom had aortic stenosis, 11 had coronary artery disease, and 2 had congestive cardiomyopathy. All were in sinus rhythm and none had clinical or haemodynamic evidence of mitral valve disease. Two patients had mild aortic regurgitation in addition to aortic stenosis, 7 had sustained previous myocardial infarction and 4 had evidence of dyskinesis on biplane left ventricular cineangiography. Only one patient was in clinical cardiac failure at the time of the study. Of the patients with aortic stenosis 5 had electrocardiographic evidence of left ventricular hypertrophy. In these patients the mean (±SEM) aortic valve gradient was 58 (±10) mmHg (7·7±1·31 kPa), the mean cardiac index was 2·91 (±0·30) l/min per m^2, and the mean aortic valve area was 0·62 (±0·10) cm^2. In the patients with coronary artery disease 3-vessel disease was present in 7 cases, 2-vessel disease in 2 cases, and single-vessel disease in 2 cases. The mean (±SEM) age of the subjects in group 1 was 30 (±1) and in group 2, 52 (±3) years.

The accelerocardiogram transducer, whose physical characteristics have been fully described (Bew *et al.*, 1971; Reuben and Littler, 1973), was attached to the chest wall overlying the fifth rib internal to the apex beat by means of an adhesive disc. An electrocardiogram recorded from praecordial leads was displayed simultaneously with the accelerocardiogram on an ultraviolet recorder (Honeywell Recording Oscillograph, Type 1185, Mark 2). All recordings were made during normal respiration with the subjects supine. Heart rate was calculated from the average of 10 consecutive RR intervals measured at a paper speed of 100 mm/s, and the amplitude of the P wave of the accelerocardiogram (Fig. 1) was also averaged over 10 cardiac cycles, each measured to the nearest millimetre, at a paper speed of 25 mm/s.

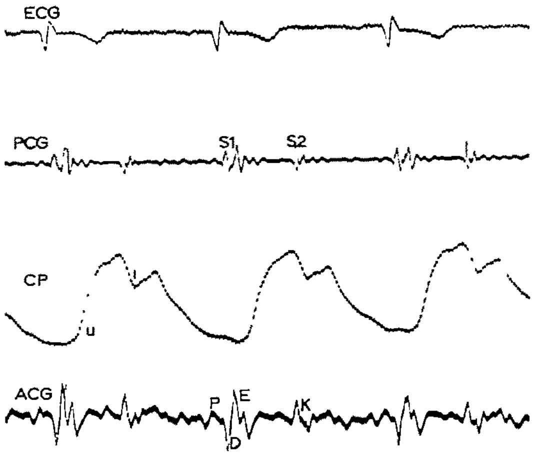

FIG. 1 *Example of accelerocardiogram tracing. From above: ECG=electrocardiogram; PCG=phonocardiogram; CP=carotid pulse; ACG=accelerocardiogram (labelled according to Rosa et al., 1961). The accelerocardiogram is of small amplitude to accommodate the phonocardiogram and carotid pulse.*

The tracings of group 1 were measured independently by 2 observers and no significant differences in the mean amplitude of the P wave occurred in any individual. For convenience, the accelerocardiographic data were expressed in microvolts, using a 0·5 millivolt square wave as a standard. No attempt was made to calibrate the tracings in units of acceleration, because variations in chest wall thickness, transducer coupling, and the position of the heart renders comparison of absolute values between subjects meaningless (Reuben and Littler, 1973). Following the convention of apex cardiography, the ratio of the amplitude of the P wave relative to the maximum systolic deflection (P/DE) was used in comparisons of resting data (Benchimol and Dimond, 1962; Gibson *et al.*, 1974; Ginn *et al.*, 1967; Voigt and Friesinger, 1970).

The patients in group 2 were studied during diagnostic cardiac catheterization after the collection of resting haemodynamic data but before angiographic studies. Beta-adrenergic blocking drugs were discontinued 72 hours before catheterization but all other drugs were administered as usual up to the time of the procedure. One hour before catheterization the patients were sedated with 5 mg diazepam (Valium, Roche) orally. In the patients with aortic stenosis left ventricular pressure was recorded by means of a Brockenbrough catheter following transseptal catheterization of the left atrium, while central aortic pressure was measured by means of a polythylene catheter 100 cm in length with an internal diameter of 0·066 cm (Formocath, Becton-Dickinson Ltd.) introduced into the right femoral artery by the Seldinger technique. The frequency response of the catheter-manometer system was flat to 20 Hz. In the remaining patients only left ventricular pressure was measured by retrograde catheterization from the right femoral artery.

Left ventricular maximum dp/dt was obtained by electronic differentiation of the pressure signal, using an RC filter network whose response was uniform to 50 Hz. Resting cardiac output was measured by the indicator dilution method, using indocyanine green as the indicator and a Waters×300 cuvette densitometer. Mean simultaneous aortic valve gradient was measured at rest and the valve area was calculated from Gorlin's formula (Gorlin and Gorlin, 1951). We used sustained isometric handgrip as a means of inducing an acute increase in left ventricular diastolic pressure, as described by previous workers (Amende *et al.*, 1972; Cohn *et al.*, 1973; Fisher *et al.*, 1973; Grossman *et al.*, 1973; Helfant *et al.*, 1971; Kivowitz *et al.*, 1971; Krayenbuehl *et al.*, 1972; Quinones *et al.*, 1974).

In the subjects of group 1, who did not undergo cardiac catheterization, handgrip was performed using a standard strain gauge dynanometer, and blood pressure was measured by sphygmomanometry, while in the patients of group 2 a partially inflated sphygmomanometer cuff was used. Each subject's maximum grip strength was first determined and each was then instructed to maintain 30 per cent maximum voluntary contraction for 3 minutes, a level of isometric exercise which has previously been shown to elicit consistent increases in heart rate and blood pressure (Fisher *et al.*, 1973; Kivowitz *et al.*, 1971; Quinones *et al.*, 1974). Care was taken to ensure that the subjects did not perform a Valsalva manoeuvre, as has been emphasized in previous studies (Fisher *et al.*, 1973; Helfant *et al.*, 1971). In the patients of group 2 peak left ventricular systolic pressure, post 'a' wave left ventricular end-diastolic pressure, and the amplitude of the 'a' wave, aortic systolic, and diastolic pressures, and left ventricular maximum dp/dt were recorded on an ultraviolet recorder (Shandon Southern Instruments Ltd., U.K.) simultaneously with the praecordial accelerocardiogram. Recordings were made before, during the final 30 seconds of, and 4 minutes after handgrip.

The results for the individual and for the group are expressed as the mean value±1 SEM. Statistical analysis was performed by Student's paired and unpaired *t* test using a PDP 11/10 computer (Digital Equipment Corporation, Maynard, Massachusetts).

Results

The results are summarized in Tables 1 to 3 and in Figs. 2 and 3.

TABLE 1 *Resting (control) data and effects of handgrip in normal subjects*

Subject		*Heart rate (beats/min)*	*LV systolic pressure (mmHg)*	*Ao diastolic pressure (mmHg)*	*P (μV)*	*P/DE (%)*
1	Control	64	118	75	155 (7)	24 (2)
	Handgrip	75	150	90	179 (19)	
2	Control	66	110	80	148 (4)	23 (1)
	Handgrip	82	130	95	216 (10)	
3	Control	82	118	74	224 (9)	33 (2)
	Handgrip	85	130	90	196 (11)	
4	Control	59	115	90	182 (11)	50 (3)
	Handgrip	75	145	105	178 (9)	
5	Control	69	90	55	169 (11)	19 (1)
	Handgrip	71	110	70	200 (11)	
6	Control	71	130	95	220 (12)	26 (2)
	Handgrip	85	160	95	228 (15)	
Group	Control	68 (3)	114 (5)	78 (6)	183 (13)	29 (5)
	Handgrip	78 (2)	139 (7)	91 (5)	200 (8)	
% Change		+13 (3)	+21 (2)	+18 (4)	+11·5 (8)	—
P		<0·005	<0·001	<0·02	>0·20	—

Figures in parentheses represent one standard error of the mean for the individual and for the group.

Conversion from Traditional to SI units: 1 mmHg≈0·133 kPa

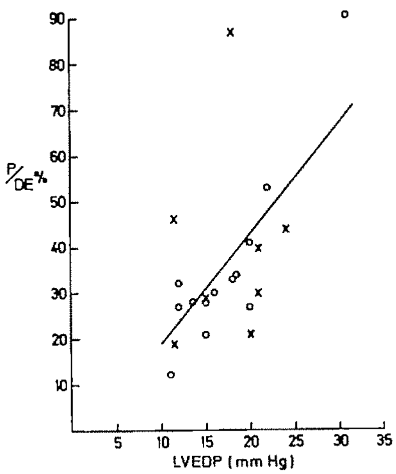

FIG. 2 *Correlation between P/DE and left ventricular end-diastolic pressure at rest. Crosses represent patients with aortic stenosis. Circles represent patients with myocardial disease.*

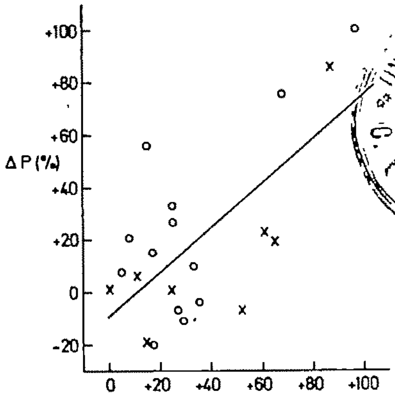

FIG. 3 *Correlation between the percentage change in the amplitude of the P wave during handgrip and the percentage change in left ventricular end-diastolic pressure. Crosses represent patients with aortic stenosis. Circles represent patients with myocardial disease.*

TABLE 3 *Regression data in Group 2*

	Regression equation	*Correlation coefficient*	*P value*
P/DE v LVEDP	P/DE= 2 4×LVEDP—5·7	0·60	<0 01
ΔP v ΔLVEDP	ΔP= 0·85×ΔLVEDP—9	0·68	<0 01

TABLE 2 *Resting (control) data and effects of handgrip in patients with heart disease*

Subject		*Heart rate (beats/min)*	*LV syst. pressure (mmHg)*	*Ao diast. pressure (mmHg)*	*LV max. dp/dt (mmHg/s)*	*LV end-diast. pressure (mmHg)*	*P (μV)*	*P/DE (%)*
7	Control	76	163	86	1870	20	228 (11)	21 (1)
	Handgrip	82	182	92	2540	23	185 (10)	
8	Control	60	210	95	1890	24	158 (6)	44 (3)
	Handgrip	79	240	120	3040	45	293 (13)	
9	Control	94	203	75	1600	18	184 (6)	87 (3)
	Handgrip	98	215	85	1800	20	200 (16)	
10	Control	65	120	70	1330	11·5	140 (6)	19 (1)
	Handgrip	73	160	87	1550	19	167 (13)	
11	Control	111	210	80	1560	21	220 (13)	30 (3)
	Handgrip	114	215	97	1900	32	204 (22)	
12	Control	72	220	65	500	11·5	205 (3)	46 (2)
	Handgrip	81	258	75	620	18·5	253 (10)	
13	Control	63	233	78	1450	21	183 (5)	40 (1)
	Handgrip	68	250	84	1650	26	184 (12)	
14	Control	81	240	90	1820	15	184 (12)	29 (2)
	Handgrip	83	250	100	1960	15	187 (12)	
15	Control	47	135	—	2000	20	254 (22)	27 (1)
	Handgrip	58	175	—	2000	21	276 (20)	
16	Control	60	190	—	1780	15	143 (7)	29 (1)
	Handgrip	62	215	—	1930	20	158 (14)	
17	Control	81	160	—	960	18·5	243 (16)	34 (2)
	Handgrip	88	180	—	1060	25	234 (13)	
18	Control	65	125	—	1820	15	121 (3)	21 (1)
	Handgrip	90	168	—	2180	29·5	245 (16)	
19	Control	53	125	—	1120	16	110 (3)	30 (2)
	Handgrip	57	140	—	1250	20	140 (8)	
20	Control	76	125	—	2360	18	210 (10)	33 (2)
	Handgrip	82	148	—	2800	21	242 (17)	
21	Control	61	120	—	2150	11	115 (4)	12 (1)
	Handgrip	71	157	—	3170	18·5	202 (22)	
22	Control	76	120	—	870	22	251 (10)	53 (3)
	Handgrip	80	130	—	1000	28	234 (11)	
23	Control	110	—	—	1100	31	377 (23)	91 (3)
	Handgrip	113	—	—	1150	40	335 (15)	
24	Control	81	117	—	1390	13·5	135 (7)	28 (2)
	Handgrip	85	137	—	1530	15·5	210 (29)	
25	Control	67	130	—	1850	20	208 (9)	41 (3)
	Handgrip	68	135	—	1790	25	277 (18)	
26	Control	70	112	—	1190	12	153 (5)	27 (1)
	Handgrip	78	140	—	1300	14	123 (5)	
27	Control	76	120	—	1840	12	120 (5)	32 (3)
	Handgrip	87	140	—	2780	13	145 (8)	
Group	Control	74 (4)	159 (10)	80 (4)	1545 (100)	17 (1)	188 (14)	37 (4)
	Handgrip	81 (3)	182 (10)	93 (5)	1855 (155)	23 (2)	214 (12)	
% Change		+9 (1·5)	+16 (2)	+16 (3)	+19 (3·5)	+34 (6)	+20 (7)	—
P		<0·001	<0·001	<0·001	<0·001	<0·001	<0·02	—

Figures in parentheses represent one standard error of the mean for the individual and for the group.

Resting data

In our patient groups a significant linear correlation existed between P/DE and left ventricular end-diastolic pressure at rest (Fig. 2, Table 3), this being largely because of an extremely good correlation in the patients with myocardial disease. When the height of the left ventricular 'a' wave was substituted for end-diastolic pressure no improvement in this correlation was observed. Though the average ratio P/DE in group 1 was 29±5 per cent (Table 1) compared with 37±4 per cent in group 2 (Table 2), these were not significantly different (P >0·30).

Handgrip

The haemodynamic effects of handgrip in the individual and in the groups as a whole are summarized in Tables 1 and 2. There were no significant differences between the groups as regards the percentage change in heart rate (P >0·20), systolic pressure (P >0·30), or aortic diastolic pressure (P >0·80).

In Group 2 the mean left ventricular end-diastolic pressure increased from 17 to 23 mmHg (2·3 to 3·1 kPa), a change of 34±6 per cent (Table 2). This change was significant (P <0·001).

In the normal subjects of group 1 the mean amplitude of the P wave of the accelerocardiogram increased from 183 to 200 microvolts during handgrip, a change of 11·5±8 per cent (Table 1), which was not significant (P >0·20) (Table 1). In group 2 the amplitude of the P wave increased from 188 to 214 microvolts (Table 2), a change of 20±7 per cent (Table 2), which was significant (P <0·02). However, the difference between the groups in the increase in the amplitude of the P wave during handgrip was not significant (P >0·30).

A significant linear correlation existed between the percentage changes in P and end-diastolic pressure during handgrip in group 2 (Fig. 3, Table 3). The correlation was not improved by substituting the percentage change in the height of the 'a' wave for the percentage change in end-diastolic pressure.

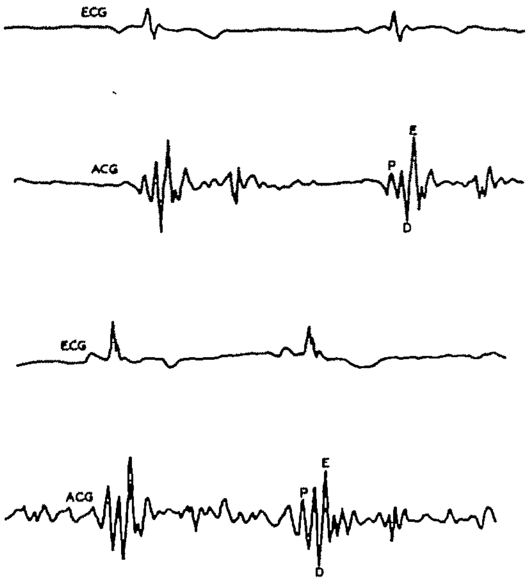

FIG. 4 *Example showing the increase in the amplitude of the P wave of the accelerocardiogram during handgrip. Top pair of records=control; lower pair=handgrip. In this example the amplitude of the P wave (measured from trough to peak) increased by 85 per cent.*

Discussion

The P wave of the praecordial accelerocardiogram has been shown to occur simultaneously with atrial systole (Luisada, 1962; Mounsey, 1959; Rosa and Kaplan, 1960; Rosa *et al.*, 1961), and its amplitude has been shown to be increased in patients with a fourth heart sound (Mounsey, 1957) and left ventricular hypertrophy (Mounsey, 1959). However, this previous work was subjectively based while the results reported in this study represent the first quantitative evaluation of the diastolic waves of the accelerocardiogram.

We have shown a linear correlation between P/DE and left ventricular end-diastolic pressure (Table 3, Fig. 2), with a correlation coefficient (r=0·60) similar to that described in previous work with the apex cardiogram (Gibson *et al.*, 1974). In general only a moderate correlation between the 'a' wave of the apex cardiogram and left ventricular end-diastolic pressure has been demonstrable, and this has been attributed to a variety of factors. Firstly, the amplitude of the 'a' wave of the apex cardiogram depends on the contribution which atrial systole makes to left ventricular end-diastolic pressure (Benchimol and Dimond, 1962; Dimond and Benchimol, 1963; Voigt and Friesinger, 1970). However, in the present study the correlation was not improved when the amplitude of the left ventricular 'a' wave was substituted for end-diastolic pressure. Secondly, the transmission of diastolic pressure waves through the chest wall depends on left ventricular wall stiffness and tension (Benchimol and Dimond, 1962; Cohn *et al.*, 1973; Gibson *et al.*, 1974; Mounsey, 1959; Rios and Massumi, 1965; Siegel *et al.*, 1972; Voigt and Friesinger, 1970) which influence the relation between diastolic pressure and praecordial pulsations, particularly in a heterogeneous group of patients, some of whom have left ventricular hypertrophy or dyskinesis.

Finally, in patients with left ventricular dilatation changes in the mechanical coupling between heart and chest wall might modify the relation between praecordial pulsations and end-diastolic pressure.

Although the average ratio P/DE in the patients was greater than that in the group of normal subjects (Tables 1 and 2), the variability within the groups was such that this was not significant (P >0·30).

The increases in heart rate, blood pressure, left ventricular maximum dp/dt, and end-diastolic pressure, which we observed in our subjects during handgrip (Tables 1 and 2), are similar to those described in previous work (Fisher *et al.*, 1973;

Grossman *et al.*, 1973; Helfant *et al.*, 1971; Kivowitz *et al.*, 1971; Krayenbuehl *et al.*, 1972). Furthermore, the increases in heart rate and blood pressure during handgrip were similar in each of our groups, suggesting that the intensity of the stress was comparable.

The amplitude of the P wave of the accelerocardiogram increased during handgrip in both groups. This was significant for the patients as a whole (P <0·02) but not for our normal control subjects (P >0·20) (Tables 1 and 2). However, we have failed to show a statistically significant difference between the groups as regards the increase in the amplitude of the P wave during handgrip (P >0·30). This might be caused, in part, by the small number of subjects studied. A better separation might also have been achieved if a more intense level of exercise had been employed. We feel, however, that the major factor accounting for our inability to discriminate between the groups is that we were compelled to express the changes in the amplitude of the P wave during handgrip in terms of a percentage, rather than in absolute units. The haemodynamic counterpart of this is obviously the percentage change in end-diastolic pressure. However, the same percentage change in end-diastolic pressure may signify a normal response in subjects with a normal resting level and an abnormal response in subjects whose end-diastolic pressure is raised at rest.

The mean increase in the amplitude of the P wave of 11·5 per cent during handgrip in the normal subjects is equivalent to a 24 per cent increase in left ventricular end-diastolic pressure (from regression equation, Table 3) which, from a normal resting level, is compatible with the increases in end-diastolic pressure observed by other workers in normal subjects during handgrip (Grossman *et al.*, 1973; Helfant *et al.*, 1971; Krayenbuehl *et al.*, 1972; Quinones *et al.*, 1974).

An increase in the amplitude of the 'a' wave of the apex cardiogram may be attributed either to an increase in the force of atrial contraction consequent upon a reduction in left ventricular end-diastolic distensibility or to an increase in left ventricular volume (Benchimol and Dimond, 1962; Gibson *et al.*, 1974; Rios and Massumi, 1965; Siegel *et al.*, 1972; Voigt and Friesinger, 1970). Whether the increase in left ventricular filling pressure which occurs during handgrip is the result of an acute change in compliance or of dilatation of the ventricle, caused by acute left ventricular failure, is uncertain (Fisher *et al.*, 1973; Grossman *et al.*, 1973; Siegel *et al.*, 1972). An increase in left ventricular size during handgrip in patients with severe myocardial disease has recently been shown (Ludbrook, Karliner, and O'Rourke, 1974), in contrast to the lack of change in normal subjects (Ludbrook *et al.*, 1974; Stefadouros *et al.*, 1974), which suggests that the increase in end-diastolic pressure in some patients may be caused, at least in part, by acute left ventricular failure. Our results, of course, do not shed any light on the mechanisms that underlie the increases in filling pressure and the amplitude of the P wave of the praecordial accelerocardiogram during handgrip, but they do suggest that accelerocardiography might be useful in monitoring changes in left ventricular end-diastolic pressure in serial studies or in response to acute interventions.

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Angiosarcoma of pericardium
Problems in diagnosis and management

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The clinical histories of two patients with angiosarcoma of the pericardium are described. Both were previously well young men who presented with cardiac tamponade caused by haemorrhagic pericardial effusions. If a pericardiectomy is undertaken for diagnosis, wide excision of the pericardium is recommended. This will provide a large specimen for histological examination and may prevent subsequent development of constriction.

Primary malignant tumours of the pericardium are rare. Over half are mesotheliomas (Dawe, Wood, and Mitchell, 1953) and the remainder are other sarcomas, including angiosarcoma. Secondary involvement of the pericardium by direct invasion from cardiac and lung neoplasms or by metastatic spread is more frequent (Harris, 1960). Thirteen cases of angiosarcoma involving the pericardium have been previously reported (Glancy, Morales, and Roberts, 1968; Hollingsworth and Sturgill, 1969; Hansson *et al.*, 1970), and two further cases are presented in this paper. They illustrate the need for an extensive pericardial excision to provide sufficient tissue for histological examination and to prevent the development of constriction.

Case reports

Case 1

Two weeks before admission a previously fit 45-year-old clerk noticed increasing exertional dyspnoea, dull central chest pain, and night sweats. He had no orthopnoea or haemoptysis. He smoked 40 cigarettes a day and had had no contact with the manufacture of plastics.

On examination he was pale and febrile (38·7°C). The jugular venous pressure was raised 12 cm from the sternal angle, the blood pressure was 90/60 mmHg (12·0/8·0 kPa) and there was 25 mmHg (3·3 kPa) pulsus paradoxus. The cardiac impulse was not palpable, but a third heart sound was heard at the apex. There was no sacral oedema and there were no added sounds in the lungs. The liver edge extended 4 cm below the costal margin. Other clinical findings were normal. The haemoglobin was 9·9 g/dl, white blood count 9300/mm^3, and platelets 150 000/mm^3; the serum sodium was 137 mmol/l, potassium 4·0 mmol/l, bicarbonate 24 mmol/l, and urea 3·0 mmol/1. On the chest film the cardiac silhouette was globular, and the electrocardiogram showed sinus rhythm with a mean frontal QRS axis of +30° and abnormal repolarization in most leads compatible with pericarditis or pericardial effusion. Tests for antinuclear factor and rheumatoid factor were negative. Blood culture was sterile. Liver function tests, prothrombin ratio, and partial thromboplastin test were all normal. Echocardiography confirmed the presence of pericardial fluid. A diagnosis of cardiac tamponade was made and 1500 ml heavily blood-stained fluid were aspirated. The fluid was sterile on bacteriological and viral culture, and no malignant cells were found.

Although he was symptomatically improved after pericardiocentesis, the signs of cardiac constriction recurred after two weeks. At operation, the pericardial sac was obliterated with fibrous adhesions, and posteriorly there were loculi of blood. The pericardium was excised to the atrioventricular groove to relieve constriction. Bacteriological and viral cultures of the pericardium were sterile. The postoperative course was uncomplicated. He received a course of external irradiation to the mediastinum and has remained well for six months.

The specimen consisted of 11 fragments of pericardium, the two largest measuring 9×5 cm, with thickness varying between 0·5 and 1 cm. Histological sections showed great thickening of the pericardium caused by organizing blood clot and fibrous tissue. There were multiple foci of malignant tumour, consisting mainly of spindle cells which formed many capillary-sized, and some larger, blood vascular spaces (Fig. 1). There were many mitoses. The appearances of this tumour were those of angiosarcoma.

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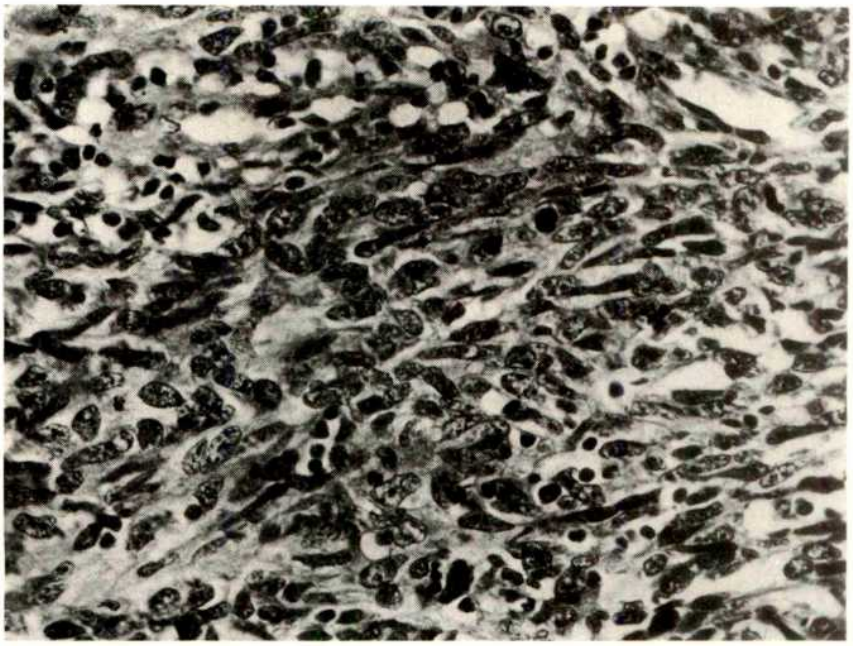

FIG. 1 *Case 1. Pericardial biopsy showing pleomorphic spindle-shaped tumour cells with capillary-sized blood spaces.* (× *390.*)

Case 2

The patient was a 20-year-old man who had been healthy until he presented with epistaxis and haemoptysis. Part of his nasal mucosa was cauterized. Four months later he was admitted to hospital complaining of malaise and pain in the right hip, epigastrium, and right hypochondrium. He had a pyrexia of 30°C. He had no industrial contact with plastics. The initial diagnosis was a viral infection.

Within one week he developed bilateral pleural effusions and peripheral oedema. The venous pressure was raised 10 cm above the sternal angle and there was 25 mmHg (3·3 kPa) of pulsus paradoxus. The blood pressure was 95/70 mmHg (12·6/9·3 kPa). Pleural and pericardial rubs were heard, but there were no cardiac murmurs. The liver was enlarged 5 cm below the costal margin. A diagnosis of cardiac tamponade was made. Thoracocentesis yielded straw-coloured fluid and pericardiocentesis heavily blood-stained fluid. He did not respond to treatment with antibiotics and in the following two weeks two further aspirations of the pericardium were performed. At this time the haemoglobin was 7·8 g/dl, white blood count 25 000/mm^3, and platelets 260 000/mm^3; the serum sodium was 130 mmol/l, potassium 3·9 mmol/l, bicarbonate 26 mmol/l, and urea 3·8 mmol/l; bilirubin 46 μmol/l; alkaline phosphatase 14 King Armstrong units/dl and AST 350 IU/l. The prothrombin ratio and the partial thromboplastin test were normal. Chest *x*-ray examination showed increase in size of the heart shadow, with bilateral pleural effusions. The electrocardiogram was normal. Blood cultures were sterile. No bacteria, acid-fast bacilli, or malignant cells were found in the pleural or pericardial aspirates. Viral studies were negative.

Neither *x*-rays after introduction of 100 ml air into the pericardium nor a right atrial angiogram showed a discrete tumour. Antituberculous therapy was begun. At thoracotomy, the pericardium was thickened, granular, oedematous, and vascular. The inner surface was red and haemorrhagic. Histological examination showed great thickening of the pericardium caused by organizing blood clot and many proliferating capillary blood vessels. Many of these vessels were lined by atypical endothelial cells showing frequent mitoses (Fig. 2). Though the possibility of angiosarcoma was considered, the evidence was thought insufficient and the histological appearances were interpreted as those of organizing blood clot and atypical granulation tissue.

Two days after operation he developed weakness of his left arm and then gradually a complete left hemiplegia. The cerebrospinal fluid contained protein 5g/l, red blood cells 160/mm^3, white blood cells 610/mm^3, and glucose 1·9 mmol/l. Right carotid angiography showed a large mass in the right posterior parietal region and a 1·5 cm leftward shift of the cerebral vessels. He became more confused and was treated with large doses of intravenous antibiotics for a possible cerebral abscess. While being prepared for operation he had a large haemoptysis. He rapidly deteriorated and died five months after the onset of his illness.

At necropsy the pericardium was thickened, with fibrous, haemorrhagic, and gelatinous material adherent to the heart, which was normal. Both main bronchi were partially obstructed by recent blood clot. The right

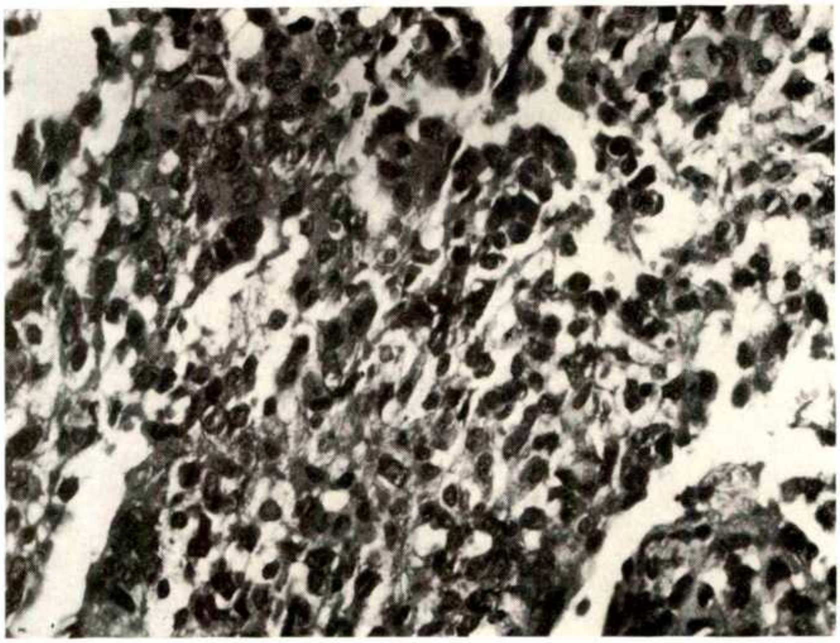

FIG. 2 *Case 2. Pericardial biopsy originally interpreted as atypical granulation tissue. (× 390.)*

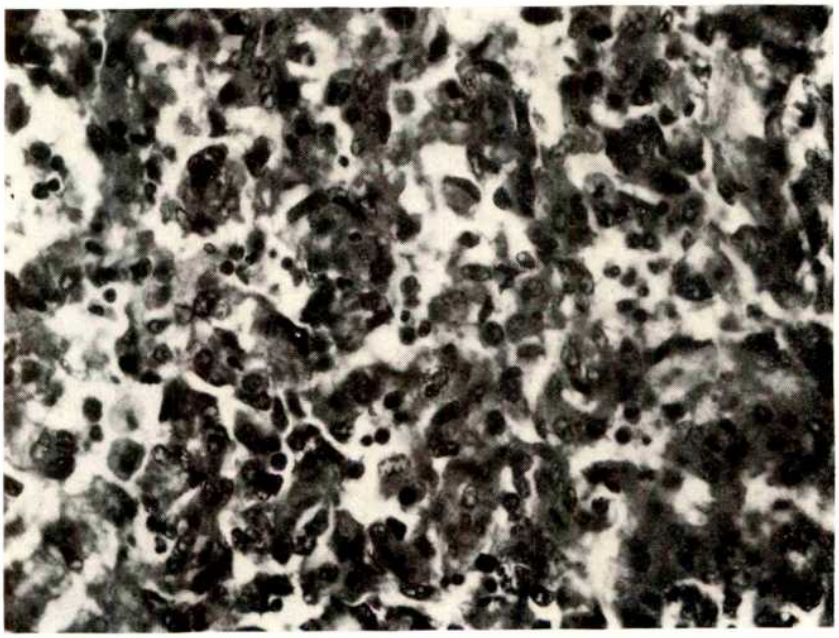

FIG. 3 *Liver metastases showing tumour cells with bizarre nuclear pattern and large blood-filled spaces. (× 390.)*

lung contained firm, spherical masses of pinkish grey tissue varying from 0·2 to 1·5 cm in diameter. The liver (2470 g) was enlarged and contained several haemorrhagic masses from 0·2 to 2 cm in diameter. A blood clot 5×5×3 cm occupied much of the parietal white matter of the right cerebral hemisphere. Microscopical examination showed haemorrhagic malignant tumour in the pericardium, lungs, and liver. The tumour was composed of solid clusters of cells with oval and spindle-shaped vesicular nuclei tending to form capillary-sized blood channels or, more rarely, cavernous blood-filled sinuses (Fig. 3). Many mitoses were present. Several sections of the brain did not show tumour, but it is possible that a small deposit was responsible for the cerebral haemorrhage.

Discussion

Angiosarcoma is a rare malignant neoplasm characterized by the presence of atypical vascular spaces lined by bizarre, malignant endothelial cells. The tumour has recently provoked much fresh interest because of the association between exposure to vinyl chloride and angiosarcoma of the liver (*British Medical Journal,* 1974). There was no history of exposure to vinyl chloride in either of our cases. Angiosarcoma has been reported in the spleen, bone, breast, uterus, heart, skin, and subcutaneous tissues. Primary angiosarcoma of the pericardium is extremely rare, but the clinical picture is surprisingly uniform (Hansson *et al.,* 1970).

The age incidence of this tumour is maximal between the third and fifth decades of life. The patients have usually been well, are mostly male, and present with chest pain, fever, and pericardial and pleural effusions, suggesting an infective process (Glancy *et al.,* 1968). Culture of the pericardial fluid for bacteria, acid-fast bacilli, and viruses, and examination for malignant cells should precede biopsy.

A formal open biopsy is required for a definitive diagnosis. Wide excision of the pericardium is necessary to avoid sampling errors. Removal of the pericardium to the atrioventricular groove provides sufficient tissue for histological examination and also frees the ventricle, thus preventing subsequent constriction. There is sometimes a conspicuous papillary proliferation of endothelial cells, with large hyperchromatic nuclei in the vessels of organizing haematomas, and this histological appearance may be very difficult to distinguish from that of angiosarcoma (Masson, 1923). This point is well illustrated by our second patient, in whom the original biopsy was interpreted as showing organizing blood clot and atypical granulation tissue, but on review of the sections in the light of the post-mortem findings, the appearance was in fact that of angiosarcoma. Constriction may be caused by organization of haemorrhagic pericardial fluid, as in the first case report, or by encasement of the heart by tumour (Glancy *et al.,* 1968).

The prognosis of patients with this tumour is extremely poor, with few surviving more than 12 months. Some success with a combination of radical excision, radiotherapy, and chemotherapy has been reported by Hollingsworth and Sturgill (1969). As the tumour was apparently limited to the pericardium in the first patient reported here, early radical excision, besides establishing the diagnosis and preventing constriction, may in conjunction with radiotherapy, alter the usual malign course of this tumour.

The second patient was under the care of Sir John Richardson, and we are grateful for his permission to publish this case. The necropsy was performed by Dr. Pauline Kahn at the National Hospital for Nervous Diseases, Maida Vale, W9, and we are grateful to Dr. R. O. Barnard for details of the microscopical findings.

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Clinical features and investigative findings in presence of mitral leaflet prolapse

Study of 85 consecutive patients

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In a 14-month period mitral leaflet prolapse was diagnosed in 85 patients by echocardiography or cine-angiography.

Chest pain alone was the presenting complaint in 30 patients and linked with palpitation, dyspnoea, or syncope in 9. Eleven presented with major neurological disturbances (9 had transient ischaemic attacks), 10 with palpitation, 4 with undue and persistent fatigue, 2 with dyspnoea, and 2 with dizziness. Seventeen were referred not because of symptoms but because of clicks and murmurs.

Overall, chest pain affected 61 patients and unless associated with coronary artery disease was not anginal. Palpitation was admitted by 42 patients; dizziness, lightheadedness, or paraesthesiae by 15, and syncope by 12.

Systolic auscultatory abnormalities were noted in 69: 25 had single clicks, 3 had multiple clicks, 19 had both click(s) and murmur, and 22 had a murmur alone.

Electrocardiography revealed ST segments flat for $>0{\cdot}10$ *s in 21, prolonged* QT_c *in 18, and T wave flattening or inversion in inferior limb and lateral chest leads in 14. The exercise stress test was abnormal in 13 of 27 patients. Mitral valve echograms showed definite mitral leaflet prolapse in 61, 'possible' prolapse in 14, and were normal in 8 patients with angiographic proof of mitral leaflet prolapse. Cardiac catheterization with left ventriculography showed prolapse of posterior mitral leaflet in 36, of both leaflets in 2, and left ventricular wall motion abnormalities in 16 cases. Selective coronary arteriography in 31 cases showed major vessel narrowing of* ≥ 80 *per cent lumen diameter in 4, all with angina.*

This consecutive series indicates that the physical event of mitral leaflet prolapse is more common than hitherto appreciated, is prominently associated with non-anginal chest pain, palpitation, and neurological disturbances, and in 90 per cent of cases could be shown echocardiographically.

A rapidly increasing number of reports on the syndrome associated with prolapse of the leaflets of the mitral valve, often suspected because of the presence of systolic clicks and/or murmurs, attests to the fascination and clinical importance of this entity (Reid, 1961; Barlow *et al.*, 1963; Criley *et al.*, 1966; Epstein and Coulshed, 1973; Jeresaty 1973a; Cobbs, 1974).

Features of this syndrome include chest pain which is often unlike 'classical' angina pectoris (Hancock and Cohn, 1966; Jeresaty, 1973a; LeWinter *et al.*, 1974), dyspnoea and fatigue (Hancock and Cohn, 1966; Barlow *et al.*, 1968; Jeresaty, 1973a), and palpitation (Hancock and Cohn, 1966; Jeresaty, 1973a). These symptoms have proved common in our own experience of patients with mitral leaflet prolapse, but we have also encountered a number of cases with neurological problems.

It is the purpose of this report to document symptoms, signs, and investigative findings in patients with mitral leaflet prolapse diagnosed in our unit and thus to help to define the clinical spectrum of this apparently common disorder.

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Subjects and methods

Our data were derived from review of the records of all patients evaluated during a 14-month period in the Cardiac Investigation Unit at University Hospital, London, Ontario, in whom the physical event of mitral leaflet prolapse was demonstrated by echocardiography or contrast cineangiography.

Data on symptoms and physical signs were transcribed from the patients' medical records. Particular care was taken to identify each patient's *presenting* symptoms and to differentiate between these and the symptoms of chest pain, palpitation, dyspnoea, fatigue, lightheadedness, dizziness, or syncope, which we specifically sought in the medical history. Where chest pain was reported, its features were recorded in detail; we accepted it as 'classical' angina pectoris only when it satisfied the criteria of 1) involving at least part of the praecordium, 2) onset related to exercise and subsequent relief with rest, and 3) visceral quality.

Standard non-fasting 12-lead electrocardiograms were recorded at rest. Twenty-seven patients underwent exercise stress testing on a motor driven treadmill according to a standardized procedure (Sheffield, 1972) of graded exercise increments, increasing their heart rate towards an age-related submaximal target rate. Resting and postexercise 12-lead electrocardiograms were recorded in 4 subsets of 3 simultaneous leads by Marquette Series 3000 equipment. Fifteen patients also had 24-hour continuous tape recording of their electrocardiogram by Holter monitor (Bleifer *et al.*, 1974) and 2 were monitored for at least 24 hours in the Coronary Care Unit.

Phonocardiograms were obtained using a piezoelectric crystal contact microphone (Litton-Hellige lightweight heart sound microphone number 217 131 01) and apex cardiograms and carotid pulse tracings with a specially constructed pneumatic system connected to a piezoelectric crystal microphone (Litton-Hellige microphone number 217 133 01). Recordings were made on a Litton Multiscriptor EK 22 5-channel chart recorder with carbon-transfer write-out.

Echocardiography was performed with the patient in the supine or slight left lateral position using a standard Unirad Series C Diagnostic Echoscope System with a 2·5 or 3·5 MHz transducer positioned in the third or fourth left intercostal space. Echocardiograms were recorded by direct photography of the multichannel oscilloscope presentation using Polaroid type 107 film and on Kodak 1895 light-sensitive paper with a 'continuous copy' Honeywell model 1856 Visicorder.

Cardiac catheterization was undertaken in 38 patients. After the measurement of the resting left ventricular end-diastolic pressure, left ventriculograms were obtained sequentially in the 30° right anterior and 45° left anterior oblique projections to assess mitral valve integrity. Additionally the tricuspid valve was assessed by right ventriculography in 8 patients, and in 31 patients selective coronary arteriography was performed.

Results

Patient population (Fig. 1)

Eighty-five patients were seen with a male:female ratio of 36:49 (1:1·4) and a peak incidence among women in the age-group 30 to 39 years. The patients' ages ranged from 15 to 76 years. Only 5 patients gave a history of childhood rheumatic fever. There were no cases of atrial septal defect (McDonald *et al.*, 1971; Betriu *et al.*, 1975)

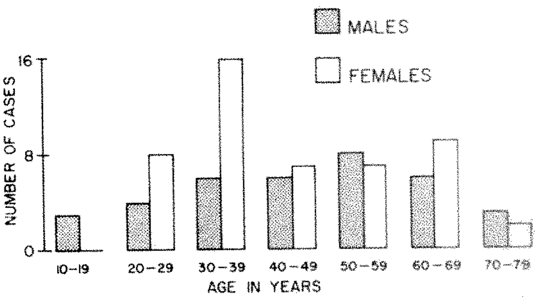

FIG. 1 *Age distribution by decades and sex distribution among 85 patients with mitral leaflet prolapse.*

Mode of presentation (Table 1)

TABLE 1 *Mode of presentation of 85 patients*

Primary presenting complaint	*No. of patients*
(A) *Symptomatic—primary presenting complaint*	
Chest pain alone	30 (35%)
Chest pain with palpitation, or dyspnoea, or syncope	9 (11%)
Palpitation ± syncope	10 (12%)
Dyspnoea	2
Undue and persistent fatigue	4
Major neurological disturbance	11 (13%)
Dizziness	2
(B) *Asymptomatic*	
Referred because click and/or murmur heard	17 (20%)
Total	85 (100%)

Group A were symptomatic with clearly identifiable presenting medical complaints and group B were asymptomatic, a systolic click and/or murmur having been discovered incidentally.

While chest pain alone (35%) or in combination with certain other symptoms (11%) was the most common problem, it is noteworthy that 13 per cent entered hospital because of a *major* neurological disturbance—by which we mean the recent unequivocal occurrence of neurological symptoms, in association with which there was at some stage documented neurological abnormality on physical examination. Among the 11 patients so presenting, the diagnosis of transient ischaemic attacks was made in 9 and 1 patient had suffered a stroke with hemiparesis; one woman with a past history of rheumatic fever had developed hemichorea, possibly related to oral contraceptives which she had taken for one year (Riddoch, Jefferson, and Bickerstaff, 1971).

Among the 17 patients presenting not because of any symptoms but rather because an auscultatory abnormality had been detected, we found that 11 were truly without significant symptomatology and the remainder admitted noticing occasional chest pain, palpitation, dyspnoea, or dizziness.

Overall incidence of certain symptoms (Table 2)

TABLE 2 *Overall incidence of certain symptoms, which includes both presenting symptoms and symptoms elicited on questioning, among all 85 patients*

Symptoms		*No. of patients*
Chest pain:		61 (72%)
as primary complaint	30 (35%)	
elicited on questioning	31 (36%)	
'classical' angina pectoris	5 (6%)	
nocturnal occurrence	13 (15%)	
Palpitation		42 (49%)
Syncope (one or more episodes)		12 (14%)
Major neurological disturbance:		13 (15%)
as primary complaint	11 (13%)	
Minor neurological disturbance (dizziness, lightheadedness, paraesthesiae)		15 (18%)

This analysis considers presenting symptoms as well as symptoms elicited on questioning. It was evident in assembling this information from all the subgroups identified in 'Mode of Presentation' that many patients did acknowledge additional symptoms in the form of chest pain, palpitation, dyspnoea, fatigue, lightheadedness, dizziness, or syncope.

Although 61 patients in all had suffered chest pain, it was a presenting symptom in only 30 and so 31 patients had to a greater or lesser extent borne it uncomplainingly. In only 5 was it acceptable classical angina. A variety of pains was described in the remainder of this group; 10 patients described their pain as 'sharp' or 'jabbing'; the pain lasted only seconds in a few but more typically lasted minutes, hours, or sometimes even weeks. Thirteen patients reported nocturnal occurrence of pain and this included 3 of the patients with classical angina of effort. One patient had, in her early 30s, experienced two episodes of pain absolutely typical of acute myocardial infarction, each time with transient T wave inversion in leads II, III, aVF, and V5 and V6, and ultimately had normal coronary arteries visualized at selective arteriography. Two men, one in his late 30's and the other in his mid 50's, suffered several episodes of severe chest pain, the features of which suggested myocardial infarction, but subsequently were found to have arteriographically normal coronary arteries.

Palpitation had been experienced by a total of 42 patients, in 7 with definite relation to chest pain, in 6 related to presyncope or syncope, in 1 with chest pain followed by syncope, and in 1 as part of the Wolff-Parkinson-White syndrome.

As well as the 11 presenting with recent major neurological disturbance, there were 2 patients who had developed hemiparesis several years earlier. Twelve had suffered one or more episodes of true syncope. Minor neurological disturbances, taking the form of dizziness, lightheadedness, or peripheral paraesthesiae, affected 15 patients.

Physical examination (Table 3)

TABLE 3 *Features noted on physical examination of 85 patients*

Feature		*No. of patients*
Marfanoid habitus		1
Auscultatory abnormalities:		68 (80%)
Single systolic click	25 (27%)	
Multiple systolic clicks	3	
Systolic click and murmur	19 (22%)	
Systolic murmur, without click	22 (26%)	
No auscultatory abnormality		17 (20%)

In general appearance only 1 patient had a Marfanoid habitus and there were no cases of the true Marfan syndrome. On auscultation a single systolic click was heard in 25 patients, multiple systolic clicks in 3, a systolic click and murmur in 19, while 22 had a systolic murmur alone. Seventeen patients had 'silent' mitral leaflet prolapse, inasmuch as there were no auscultatory abnormalities at any time. The 'silent' group underwent cardiac investigation because of some of the symptoms alluded to earlier.

Standard electrocardiography (Table 4)

In only 3 cases was the permanent stable rhythm other than sinus. One 76-year-old man, the oldest person in the study, had atrial fibrillation with a typical mitral insufficiency pansystolic murmur and echocardiographic and radiological evidence of left atrial and ventricular dilatation; though his echocardiogram showed a thin pliable anterior mitral leaflet, mitral calcification was visible fluoroscopically. A 66-year-old woman had atrial flutter, with

TABLE 4 *Commonest abnormalities in 12-lead electrocardiograms in 85 patients*

Abnormality	*No. of patients*
Small septal Q waves (depth $<0{\cdot}5$ mm in at least V5 or V6)	24 (28%)
QT$_c$ interval prolonged (Bazett's formula QT$_c$ = measured QT/$\sqrt{\text{R–R}}$)	18 (21%)
ST segments flat for $>0{\cdot}10$ s:	
a) lateral chest leads only	15 (18%)
b) lateral chest and some limb leads	6 (7%)
T waves flat or inverted in inferior limbs and some chest leads	14 (16%)
Amplitude RV5 or V6 or SV1 or V2 >25 mm (only 3 with ST—T changes of left ventricular hypertrophy)	11 (13%)

3:1 block and right bundle-branch block: cardiac catheterization revealed a thick-walled left ventricle with normal sized cavity and mitral leaflet prolapse without mitral regurgitation, aortography showed normal patency of the proximal parts of the coronary arteries, and echocardiography showed a pliable prolapsing mitral valve and normal sized left atrium. The third of these cases was a 57-year-old man with the pattern of anteroseptal myocardial infarction of indeterminate age and a low atrial or junctional rhythm with inverted P waves in II, III, and aVF. Four patients manifested ventricular ectopic beats, and in 3 of these the premature beats, when present, produced a bigeminal rhythm.

Two patients had the 'P mitrale' and a prominent P terminal vector in V1, indicative of left atrial enlargement, without any demonstrable mitral regurgitation on left ventriculography. Left anterior hemiblock was noted in 2 subjects. Minor intraventricular conduction defect, manifested by terminal QRS slurring with normal QRS duration, was present in 3 cases. Right bundle-branch block in 2 more cases was the only other intraventricular conduction abnormality. Left ventricular hypertrophy by voltage criteria alone (Lipman, Massie, and Kleiger, 1972) was seen in 8 patients and in 3 further there were additional ST segment and/or T wave changes. Poor R wave progression in V1 to V3 was present in 4 patients without any evidence of hypertrophy or conduction disturbance. Two patients showed the healed anteroseptal myocardial infarction pattern. Prominent Q waves, of depth ≥ 2 mm, were present in V6 in 2 patients while small ($<0{\cdot}5$ mm deep in I, V5 or V6) or absent septal Q waves featured in 24 and 14 cases, respectively. ST segments, flat for 0·10 s or longer, were noted in 15 patients in lateral chest leads, with an additional similar finding in some of the limb leads in 6; 1 patient had hortizontal ST segments in II, III, and aVF only. Depressed ST segments were

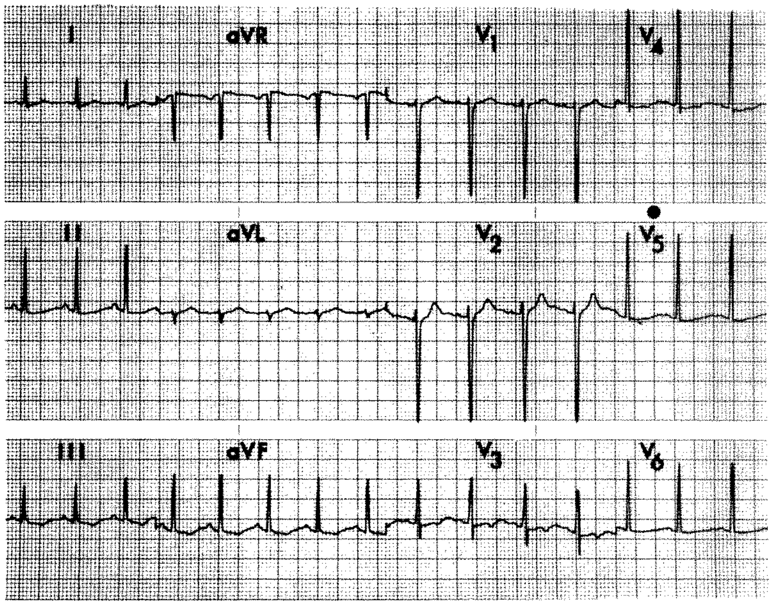

FIG. 2 *Resting electrocardiogram, of standard 1 cm/mV calibration throughout, from a 20-year-old man with mitral leaflet prolapse. The tracing is unequivocally abnormal, with T wave flattening in leads II and V6 plus T wave inversion in leads V3 to V5. The voltage changes of left ventricular hypertrophy are also present* ($SV_2 = 27$ *mm*).

were present in lateral chest leads in 4 cases, 1 with left ventricular hypertrophy. Excluding the 2 cases of old infarction pattern, flat or inverted T waves were noted in chest leads (usually V4 to V6) and inferior limb leads in 14 patients (Fig. 2); similar T wave abnormality was confined to chest leads in 1 patient, and to II, III, and aVF in 2 patients. Peaked T waves, probably a normal variant, were present in mid and lateral chest leads in 4 cases. Rate-corrected QT interval (QT_c) was prolonged (men >0·42 s; women >0·43 s) in 18 patients. Four patients showed U waves of 40 to 60 per cent of the T wave amplitude.

Electrocardiographic monitoring

Fifteen ambulatory patients were monitored for periods of at least 24 hours with the Holter tape system; 5 manifested arrhythmias and 1 showed periodic ST segment depression. The arrhythmias were 1) many junctional premature beats, 2) periods of sinus tachycardia with frequent junctional premature beats, 3) paroxysms of atrial fibrillation, 4) occasional solitary multifocal ectopic beats plus a few seconds of ventricular tachycardia, and 5) runs of supraventricular tachycardia at rates up to 140 per minute in a 19-year-old man with the Wolff-Parkinson-White abnormality.

Two patients were monitored in bed in our coronary unit for over 24 hours and no abnormality was detected in one while the other manifested frequent ventricular premature beats.

We recorded major rhythm disturbance in 2 other cases. A 23-year-old man had episodes of ventricular tachycardia and of supraventricular tachycardia, unresponsive to pharmacological anti-arrhythmic therapy and requiring electrical cardioversion on several occasions, and at other times also manifested continuous ventricular bigeminy. The tracing from this patient between arrhythmic episodes looked normal and is reported as such in Table 4; one 24-hour Holter tape recorded showed no abnormality. A 25-year-old woman developed palpitation while in hospital, and a 12-lead electrocardiogram showed a regular apparently supraventricular rhythm at a rate of 210 per minute.

TABLE 5 *Results of treadmill submaximal exercise stress testing in 27 patients*

Feature		*No. of patients*
Achieved >90 per cent predicted maximum heart rate without significant symptoms		15 (56%)
Exercise terminated prematurely:		12 (44%)
a) chest pain	6	
b) striking fatigue	3	
c) ventricular arrhythmia	2	
d) considerable ST segment depression in V4 to V6	1	
Postexercise ST segment abnormality:		13 (48%)
a) depressed >1 mm for >0·08 s, horizontal or downsloping, during first 6 min	2*	
b) flat for >0·08 s, up to 8 min or beyond	6	
c) flat for >0·08 s, immediately or at 2 min only	2	
d) flat for >0·08 s, only after at least 6 min	2	
e) cupping, or spoon-shaped sagging, up to 10 min	1	

*Both had coronary artery disease with ≥ 80 per cent luminal width narrowing of a major vessel.

Treadmill exercise stress electrocardiography (Table 5)

Twenty-seven subjects underwent our submaximal exercise stress test. Only 15 could complete the test achieving greater than 90 per cent of their predicted maximum heart rate without developing any chest pain or inappropriate dyspnoea. Exercise was terminated in 6 because of onset of chest pain similar to their spontaneous symptoms, 3 were very fatigued, 1 exhibited striking ST segment depression in the V4 to V6 leads during exercise, 1 developed frequent ventricular bigeminy, and 1 developed ventricular tachycardia. ST segment changes were assessed according to the Finnish criteria (Cumming *et al.*, 1973).

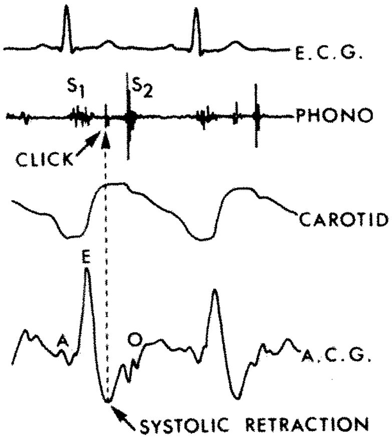

FIG. 3 *Simultaneous recording of electrocardiogram (ECG), phonocardiogram (PHONO), carotid artery pulse (CAROTID), and apex cardiogram (ACG) from a 34-year-old woman. The first heart sound (S_1), second heart sound (S_2), and A, E, and O points of the apex cardiogram are labelled. Systolic retraction of the apex cardiogram is seen to occur precisely coincident with a click just after the midpoint of systole.*

Abnormal postexercise electrocardiograms were noted in 13 patients, including all those with chest pain and with depressed ST segments and bigeminy during exercise. Ten patients developed ST segments horizontal for >0·08 s and 1 developed sagging of the ST segments in leads II and V4 to V6. Only 2 had the classical ischaemic transient flat or downsloping ST segment depression of >1 mm for >0·08 s after exercise (Sheffield and Roitman, 1975) and both had severe coronary artery disease. The changes always occurred in inferior limb and/or mid and lateral chest leads.

Phonocardiograms and apex cardiograms (Table 6)

TABLE 6 *Phonocardiogram results in 44 patients, and apex cardiogram results in 19 patients*

Feature	*No. of patients*
Timing of clicks on phonocardiograms:	
early systole	6
mid systole	16
late systole	6
diastole	none
Systolic retraction on apex cardiograms:	
present	14
absent	5

Forty-four patients had phonocardiograms and as well as confirming the presence of single, or occasionally multiple, systolic clicks this investigation also showed that when a systolic murmur was present its timing could be early systolic or pansystolic but most commonly was mid or late systolic. The timing of the clicks was most often mid systolic, as in 16 patients, but in 6 patients was early systolic and in a further 6 was late systolic. Four patients had multiple clicks.

Systolic retraction was seen in 14 of a total of 19 apex cardiograms. When a click was recorded on a simultaneous phonocardiogram it could be seen to be coincident with the nadir of apex retraction (Fig. 3), as shown by Epstein and Coulshed (1973) and Spencer, Behar, and Orgain (1973).

Echocardiography (Table 7)

Of the 85 patients, 83 were studied echocardiographically and 61 showed abnormalities of the mitral valve closure line considered diagnostic for mitral leaflet prolapse (Shah and Gramiak 1970; Dillon *et al.*, 1971; DeMaria *et al.*, 1974; Popp *et al.*, 1974; Boughner, 1975). Thirty-five showed a deep posterior curvature of the closure line beginning in midsystole (Fig. 4B) and 26 showed a multiecho systolic closure line, concave through-

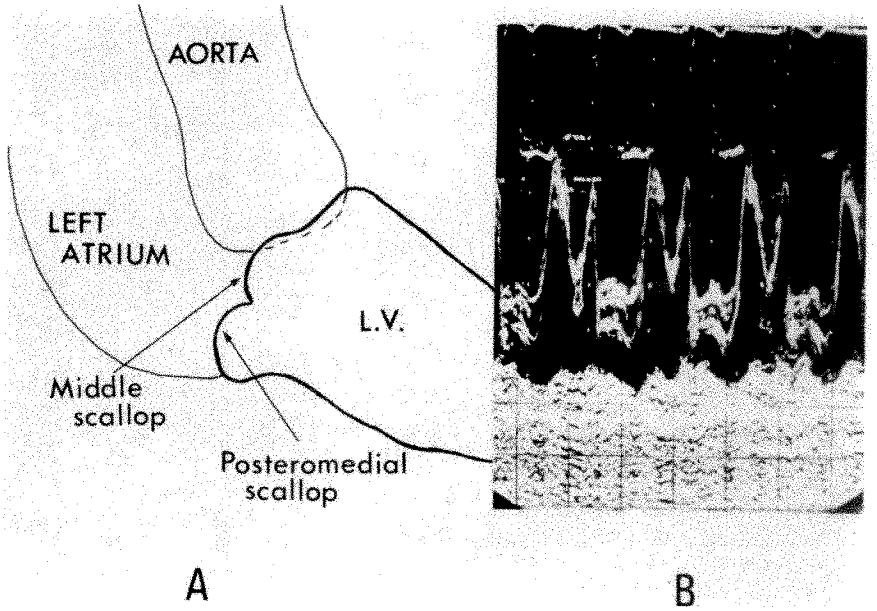

FIG. 4 *Appearances of mitral leaflet prolapse. A) Silhouette of systolic left ventricular (L.V.) angiogram, traced from projection of the 30° right anterior oblique film, with posteromedial commissural and middle scallops of posterior mitral leaflet bulging into left atrium. B) Mitral valve echogram showing deep posterior (i.e. downwards in picture) curvature of multiecho closure line during systole.*

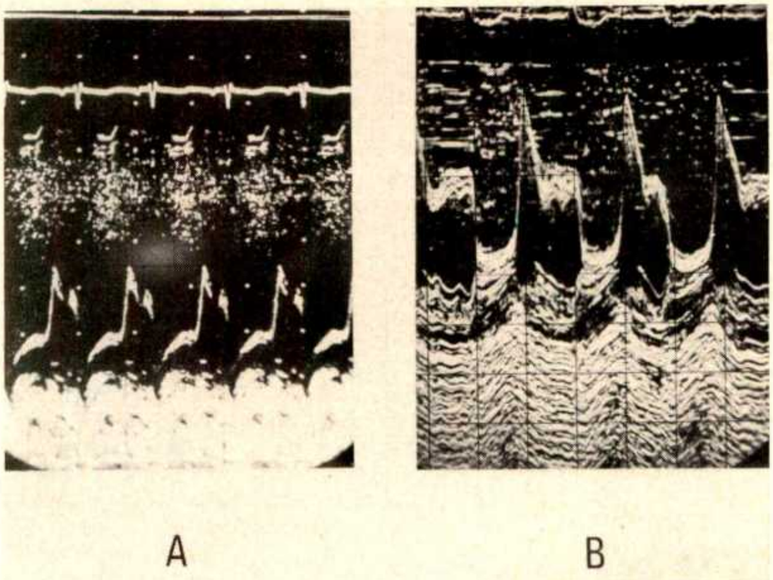

FIG. 5 *Other appearances of mitral echogram in mitral leaflet prolapse (MLP). A) Late systolic minor downturning of closure line in patient with MLP shown on angiography; this pattern we classify as 'possible MLP'. B) Multiecho closure line, concave or sagging throughout systole, indicative of definite MLP.*

TABLE 7 *Mitral valve echogram results in 83 patients*

Interpretation of echogram	*No. of patients*
Definite mitral leaflet prolapse	61 (73%)
'Possible' mitral leaflet prolapse	14 (17%)
Normal mitral systolic closure line	8 (10%)
Total	83 (100%)

out systole (Fig. 5B). Of the remainder, 14 showed a pattern that we classified as 'possible' mitral leaflet prolapse with a minor late systolic downturning of the systolic closure line (Fig. 5A) and the other 8 patients had a normal mitral echogram with smooth, progressive anterior migration of the closure line throughout systole. The 8 patients with normal echograms all showed mitral leaflet prolapse on left ventriculography. All patients with 'possible' or definite mitral leaflet prolapse who underwent left ventriculography showed clear angiographic evidence of prolapse, and this included 12 of our 14 'possible' mitral leaflet prolapse cases.

Cardiac catheterization (Table 8)

The left ventriculograms were assessed for evidence of mitral leaflet prolapse (Criley *et al.*, 1966; Ranganathan *et al.*, 1973; Boughner, 1975). Posterior leaflet prolapse was seen in all cases with various permutations of involvement of postero-

TABLE 8 *Findings at cardiac catheterization in 38 patients*

Procedure and finding		*No. of patients*
Left ventriculography		
Mitral leaflet prolapse		38 (100%)
1) Posterior leaflet involved		
a) Posteromedial commissural scallop only	20	
b) Posteromedial commissural and middle scallops	4	
c) Posteromedial and antero-lateral commissural scallops	4	
d) Triscallop involvement	10	
2) Anterior leaflet also involved	2	
Mitral insufficiency by angiographic appearance		7 (18%)
1) Severe	2	
2) Moderate	2	
3) Mild	2	
4) Trivial	1	
Wall motion abnormalities		16 (42%)
Right ventriculography (in 8 of 38 patients)		
Tricuspid leaflet prolapse		3 of 8 (38%)
Selective coronary arteriography (in 31 of the 38 patients)		
Normal		26 (83%)
Occlusive lesions		5 (16%)
1) >75% narrowing of major vessel	4	
2) 40% narrowing of major vessel	1	

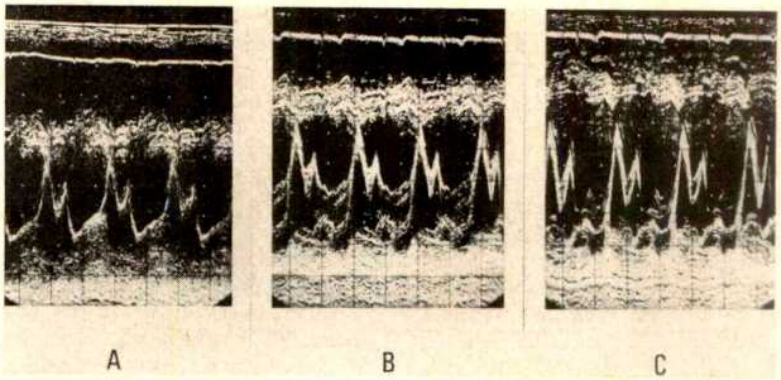

FIG. 6 *Mitral echograms obtained sequentially during same examination of one patient illustrating importance of transducer positioning. A) Apparently normal systolic closure line. B) Multiecho closure line, concave throughout systole, which is indicative of definite prolapse. C) Abrupt downturning of the systolic closure line in early to midsystole, again indicative of definite prolapse.*

medial commissural scallop, middle scallop, or anterolateral commissural scallop. Prolapse of posteromedial commissural scallop alone occurred in 20 patients, of posteromedial commissural scallop and middle scallop in 4 (Fig. 4A), of posteromedial and anterolateral commissural scallops (Fig. 7) in 3, of all 3 scallops in 10, and of anterolateral commissural scallop alone in 1. Two patients also had prolapse of the anterior mitral leaflet. Among 8 patients in whom the tricuspid valve was angiographically assessed, 3 were found to have prolapse of this valve (Gooch *et al.*, 1972a). Mitral regurgtaition was evident in 7 patients and was severe in 2 (both with triscallop posterior leaflet prolapse), moderate in 2 (1 with triscallop and 1 with posteromedial commissural scallop and middle scallop posterior leaflet prolapse), mild in 2 (1 with triscallop and 1 with posteromedial and anterolateral commissural scallop posterior leaflet plus anterior leaflet prolapse), and trivial in 1 (with posteromedial commissural scallop prolapse). Left ventriculograms in 16 of the cases showed ab-

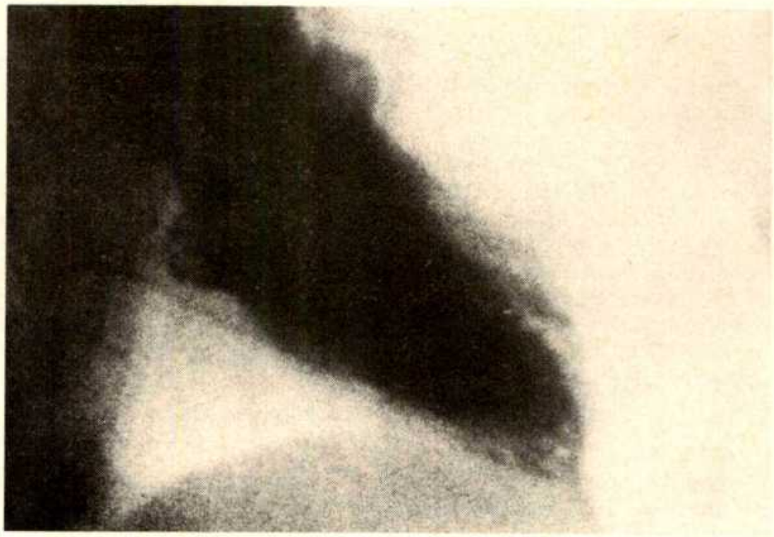

FIG. 7 *Midsystolic frame from left ventriculogram filmed in 30° right anterior oblique projection showing the prominent bulges of anterolateral commissural scallop (upper bulge) and posteromedial commissural scallop (lower bulge) posterior mitral leaflet prolapse.*

normalities of wall motion, most commonly segmental diastolic dyskinesis of the anterolateral left ventricular wall.

Left ventricular end-diastolic pressures before contrast injection were < 12 mmHg ($< 1 \cdot 6$ kPa) in 27 subjects and ≥ 12 mmHg ($\geq 1 \cdot 6$ kPa) in the remaining 11.

Selective coronary arteriography in 31 cases showed occlusive lesions in 5. Four had ≥ 80 per cent luminal width narrowing of at least 1 major vessel and all of these had angina. Another, with a 40 per cent constriction of the left anterior descending coronary artery, had not experienced angina.

Discussion

We have used the term 'mitral leaflet prolapse' in preference to other designations such as 'mitral valve prolapse' or the 'systolic click—murmur syndrome', for it is a succinct and precise description of the phenomenon which affects the leaflets rather than the whole structure of the mitral valve and it need not be associated with clicks or murmurs (Jeresaty, 1973a; DeMaria *et al.*, 1974). Detailed discussion of the mechanisms responsible for various features associated with mitral leaflet prolapse, many of which are still speculative or controversial, is beyond the scope of this paper and is not attempted; attention is directed to the reviews by Jeresaty (1973a) and Cobbs (1974) which deal with the subject. None of our patients required valve replacement and no mitral valve material has become available for pathological examination.

Patient population

Our sample of 85 patients presenting consecutively in one non-paediatric unit over a 14-month period shows the physical event of mitral leaflet prolapse to be relatively common. Greenwald (1974) reported that more than 12 per cent of patients referred to a Norwalk, Connecticut community hospital's echocardiographic laboratory had mitral leaflet prolapse and this supports our contention that the disorder is much commoner than hitherto appreciated. The preponderance of women among our patients and the peak incidence among women in the fourth decade of life follows the pattern of other series (Hancock and Cohn, 1966; Barlow *et al.*, 1968; Jeresaty, 1973a).

Mode of presentation

Chest pain, either alone or together with other symptoms, was the presenting symptom in 46 per cent of our patients and is the most common presenting complaint in association with mitral leaflet prolapse. Dyspnoea or undue and persistent fatigue brought 6 of the 85 patients to our attention and have been noted by Jeresaty (1973a) often to be the presenting symptoms in mitral leaflet prolapse. One patient, who presented with general malaise, including fatigue, was ultimately felt to have culture-negative endocarditis and had a good therapeutic response to penicillin and streptomycin. We had no cases of culture-positive endocarditis, though as a complication of mitral leaflet prolapse it is well known, and prophylaxis against bacterial endocarditis is advisable (Barlow *et al.*, 1968; Jeresaty, 1973a; Allen, Harris, and Leatham, 1974; Cobbs, 1974; Lachman *et al.*, 1975).

Thirteen per cent of our patients presented with recent major neurological disturbances. We are unaware of previous recognition of any relation between mitral leaflet prolapse and transient ischaemic attacks but careful auscultatory and echocardiographic assessment of all patients with evidence of transient cerebral ischaemia now seems warranted. Among those presenting primarily with neurological disturbances, carotid angiography was carried out in 5, showing abnormalities in only 1 (occlusion of the left posterior cerebral artery), and aortic arch angiography in 2 (normal findings in 1 and complete occlusion of the origin of the left common carotid artery in the other).

Overall incidence of certain symptoms

The primacy of chest pain among the symptoms associated with mitral leaflet prolapse is evident, with 72 per cent of our patients so afflicted, a higher prevalence than the 61 per cent found by Jeresaty (1973a) or the 35 per cent found by Hancock and Cohn (1966). The statement (Jeresaty 1973a) that, 'it was usually ill-defined, left precordial, sharp, and either fleeting or lasting several hours' serves well to describe the pain of the majority of our patients.

Our 5 patients with angina underwent coronary arteriography, 4 showing greater than 75 per cent narrowing of at least one coronary artery and the fifth having normal coronaries but left ventricular dilatation and severe mitral regurgitation. This suggests that coronary artery disease be suspected whenever a history of classical angina is elicted in a patient with mitral leaflet prolapse. It fits well with the broader concept of mitral leaflet prolapse resulting from a variety of pathological processes (Roberts, Dangel, and Bulkley, 1973), including papillary muscle ischaemia consequent upon coronary artery disease (Steelman *et al.*, 1971).

Chest pain of dramatic severity, mimicking the pain of myocardial infarction, had occurred in 3 of our patients and all 3 were found to have normal coronary vessels by selective arteriography. Gulotta *et al.* (1974) have 12 similar cases.

It is probable that the palpitation experienced by 49 per cent of our patients, 48 per cent of Hancock and Cohn's (1966) patients and 46 per cent of Jeresaty's (1973a) patients is the symptomatic declaration of the arrhythmias which are acknowledged frequently to be associated with mitral leaflet prolapse and rarely to be the cause of sudden death therein (Hancock and Cohn, 1966; Pocock and Barlow, 1970; Jeresaty, 1973a; Shappell *et al.*, 1973; Cobbs, 1974). One of our patients, a 47-year-old man, died suddenly 20 months after Holter tape monitoring had revealed a brief run of ventricular tachycardia; he was receiving oral procainamide 500 mg 6-hourly. Syncope, as experienced by 14 per cent of our patients, probably also has an arrhythmic basis.

It is difficult to draw the fine distinction between neurotic symptoms and certain minor symptoms, especially neurological, which may be genuinely and accurately reported by a perceptive patient. Hancock and Cohn (1966) and Jeresaty (1973a) reported symptoms of 'neuropsychiatric' or 'psychiatric' type in 38 per cent and 15 per cent of their patients with mitral leaflet prolapse, respectively. Shappell, Orr, and Gunn (1974) found significant psychopathology in only 1 of 8 symptom-free patients with mitral leaflet prolapse but in 5 of 6 symptomatic patients with mitral leaflet prolapse.

General physical examination

The occurrence of mitral leaflet prolapse in Marfan's syndrome is well documented (Hancock and Cohn, 1966; Pocock and Barlow, 1970; Roberts *et al.*, 1973). It appears unlikely, however, that, in general, mitral leaflet prolapse could be a *forme fruste* of the Marfan syndrome.

Auscultation and phonocardiography

Systolic clicks and murmurs were for many years the key features by which mitral leaflet prolapse could be diagnosed and so determined the cases making up most series before that of Jeresaty (1973a). The increasing availability of echocardiography has led to the recognition of 'silent' mitral leaflet prolapse, as in 20 per cent of our patients and 12 per cent of Jeresaty's (1973a) patients. When a group of 25 patients with angiographically and echographically shown mitral leaflet prolapse had phonocardiograms performed no systolic click or murmur could be shown in 42 per cent of them (DeMaria *et al.*, 1974). Postural changes in the timing and intensity of the systolic clicks and murmurs of mitral leaflet prolapse (Barlow *et al.*, 1968; Epstein and Coulshed, 1973; Fontana *et al.*, 1975) were seen in a number of our patients, and as well as auscultation with the patient standing (Cobbs, 1974) we also commend listening, with the patient sitting forward.

Standard electrocardiography

The range of disturbances of rhythm, T wave polarity and contour, ST segment slope and level, QT_c interval, and U wave prominence revealed in the tracings from our series of patients confirms the pattern of electrocardiographic abnormalities already established (Barlow and Bosman, 1966; Hancock and Cohn, 1966; Engle, 1969; Pocock and Barlow, 1970; Jeresaty, 1973a; Lobstein *et al.*, 1973; Cobbs, 1974).

Voltage criteria for left ventricular hypertrophy, present in 8 of the patients in this series without any concomitant ST segment and/or T wave abnormalities, are insufficient for the diagnosis of left ventricular hypertrophy (Lipman *et al.*, 1972). Poor R wave progression in V1 to V3 and small or absent septal Q waves may be encountered in normal adults, with an incidence comparable to that discovered in this group of patients with mitral leaflet prolapse (Simonson, 1961; Horan and Flowers, 1972).

The QT_c interval was 0·43 s or longer in 73 per cent of Hancock and Cohn's (1966) patients and was 0·45 s in a 27-year-old woman with recurrent and eventually fatal ventricular fibrillation (Shappell *et al.*, 1973). Gooch *et al.* (1972b) had 7 cases with mitral leaflet prolapse with QT interval prolongation, but 3 of these were taking quinidine. Moderate prolongation of the QT_c is considered to be a standard electrocardiographic feature of mitral leaflet prolapse by Cobbs (1974). A long QT interval, which represents delayed ventricular repolarization and so prolongation of the vulnerable period for ventricular arrhythmia, is associated with syncope and ventricular fibrillation in certain inherited disorders (Vincent, Abildskov, and Burgess, 1974; Schwartz, Periti, and Malliani, 1975). Beta-adrenergic blocking agents and stellate ganglionectomy have abbreviated the QT interval in these syndromes with partial or complete suppression of ventricular arrhythmias. Intravenous propranolol did not alter the prolonged QT_c of one patient with mitral leaflet prolapse (Shappell *et al.*, 1973). We found no correlation between QT_c prolongation and arrhythmias in individual patients. Propranolol has relieved the symptoms of chest pain and palpitation in some of our patients and is recommended antiarrhythmic therapy by Pocock and Barlow (1970), Jeresaty (1973a), and Cobbs (1974). However, Cobbs (1974) denies its efficacy in the chest pain of mitral leaflet prolapse.

Treadmill exercise stress electrocardiography

The provocation of ventricular arrhythmias in patients with mitral leaflet prolapse subjected to exercise testing is well known (Pocock and Barlow, 1970; Del Rio *et al.*, 1971; Gooch *et al.*, 1972b; Sloman, Wong, and Walker, 1972; Jeresaty, 1973a), but in our series was less frequent than expected. Our 48 per cent incidence of ST segment abnormalities after exercise accords with the experience of Del Rio *et al.* (1971), Sloman *et al.* (1972), and Jeresaty (1973a). The long-lasting, evanescent, or delayed postexercise ST segment change evident in 11 of our patients not known to have coronary insufficiency (Table 5) is highly unusual in patients with angina pectoris caused by coronary artery narrowing (Wood *et al.*, 1950; Sheffield and Roitman, 1975).

Echocardiography

The utility of mitral valve echography in the diagnosis of mitral leaflet prolapse is well established (Feigenbaum, 1973; Cobbs, 1974; DeMaria *et al.*, 1974; Joyner, 1974; Popp *et al.*, 1974). Feigenbaum (1973) states that the echocardiographic findings are quite specific and that cardiac catheterization is unnecessary to confirm a diagnosis. We agree with the specificity of a positive test but found 10 per cent false negative mitral echograms and a further 15 per cent showing only minor abnormalities of the systolic closure line. Normal mitral echograms in confirmed mitral leaflet prolapse cases have been noted previously (Kerber *et al.*, 1971; DeMaria *et al.*, 1974), and the importance of careful transducer positioning and scanning is illustrated in Fig. 6. We have shown (Boughner, 1975) that the accuracy of the mitral echogram depends to a considerable extent on the amount of posterior leaflet involvement. The echogram readily detects biscallop or triscallop posterior leaflet prolapse, but single scallop posterior leaflet prolapse may be difficult to detect and can be missed.

Cardiac catheterization

Since mitral leaflet prolapse could be shown angiographically in every patient in whom the mitral echogram had the definite or 'possible' mitral leaflet prolapse pattern, the merit of this direct approach to visualizing the deformity and malfunction of the valve is confirmed. We were convinced of anterior leaflet prolapse in only 2 of our patients, but it is acknowledged that overlap of the mitral leaflets creates difficulties in identifying anterior leaflet prolapse in left ventriculograms (Kittredge *et al.*, 1970; Jeresaty, 1971). Gooch *et al.* (1972b) did not report it in any of their 23 patients studied angiographically and others have not attempted the differentiation in single plane (Popp *et al.*, 1974) or biplane studies (DeMaria *et al.*, 1974).

Mitral regurgitation among our patients appeared severe in only 2 cases, and in total only 7 had any evidence of mitral regurgitation. This illustrates that in at least one sense our group of patients had a milder form of the mitral leaflet prolapse disease complex. Among Jeresaty's (1973a) 39 patients studied angiographically, 20 had mitral insufficiency, 8 being severe and 5 mild, and Gooch *et al.* (1972b) reported angiographically demonstrable mitral insufficiency in 21 of 23 patients with mitral leaflet prolapse.

The 11 patients (29%) with LVEDP ≥12 mmHg (1 6 kPa) were not predominantly those with mitral regurgitation or significant coronary artery narrowing—perhaps a reflection of the myocardial dysfunction reported in some cases of mitral leaflet prolapse (Gooch *et al.*, 1972b; Gulotta *et al.*, 1974).

Left ventricular wall motion abnormalities in 42 per cent of our patients catheterized resemble closely those described by Gooch *et al.* (1972b) in 17 of their 23 subjects. Most characteristic has been the early diastolic dyskinetic bulging of the middle portion of the anterolateral left ventricular wall, but dysynergy of the posteroinferior wall during systole has also been observed.

Unless classical angina is present it appears that fully patent major coronary arteries are a standard finding in mitral leaflet prolapse, as in 9 of 10 cases (Gooch *et al.*, 1972b), 26 of 27 cases (Jeresaty, 1973b), 5 of 5 cases (Lobstein *et al.*, 1973) and 26 of 26 cases (Gulotta *et al.*, 1974). Nevertheless mitral leaflet prolapse may coexist with the common primary condition of atheromatous coronary artery narrowing.

Conclusion

Mitral leaflet prolapse is a disturbance of coaptation of the mitral leaflets during ventricular systole, with prolapse of the posterior or, more rarely, both leaflets into the left atrium; in the majority of cases it can be shown by echocardiography, without false positive results. We have found that the physical event of mitral leaflet prolapse occurs commonly and is not always associated with clicks or murmurs. A predilection for certain symptoms, inlcuding chest pain, palpitation, dizziness, syncopc, and other transient neurological disturbances, is evident in those with mitral leaflet prolapse. The varied pathogenesis (Roberts *et al.*, 1973; Cobbs, 1974) must cleary be a mrjor determinant of prognosis but in most of our cases we find ourselves ignorant of the precise nature of the mitral abnormality, let alone the mechanism of production of the various symptoms. For most patients with mitral leaflet prolapse the prognosis appears good (Allen *et al.*, 1974), but this is tempered by knowledge of the few who die suddenly with arrhythmias, have worsening mitral regurgitation, develop endocarditis, or, as we have shown, suffer neurological disturbances.

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Unstable angina pectoris
Clinical, angiographic, and myocardial scintigraphic observations[1]

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The clinical, left ventricular and coronary angiographic data, and the technetium-99m stannous pyrophosphate (^{99m}Tc-PYP) myocardial scintigraphic results are presented in 31 patients with unstable angina pectoris. One-third of these patients had positive ^{99m}Tc-PYP myocardial scintigrams in a pattern suggesting limited and diffuse subendocardial necrosis. The positive ^{99m}Tc-PYP myocardial scintigrams occurred without diagnostic electrocardiographic and cardiac enzyme changes suggestive of myocardial infarction; positive scintigrams seemed to occur more commonly in patients with continuing pain after admission and in those without previous history of myocardial infarction. The positive ^{99m}Tc-PYP myocardial scintigrams did not correctly predict coronary anatomical patterns except that positive scintigrams occurred only in patients with coronary artery disease. Neither did the positive scintigrams necessarily occur in that group of patients with the poorest ventricular function though the 2 patients with the lowest ejection fractions both had positive ^{99m}Tc-PYP myocardial scintigrams. Finally, when positive ^{99m}Tc-PYP scintigrams are the only evidence suggestive of limited subendocardial infarction in patients with unstable angina pectoris, they do not appear to have any prognostic significance in terms of longevity or response to pharmacological or surgical therapy, though the follow-up period so far is short.

Unstable angina pectoris is an expression of ischaemic heart disease comprising several heterogeneous syndromes intermediate between chronic, stable angina and acute myocardial infarction (Sampson and Eliaser, 1937; Beamish and Storrie, 1960; Wood, 1961; Resnik, 1962; Vakil, 1964). Attempts to define its natural history have been beset by imprecise and variable diagnostic criteria, differences in patient populations, and in some instances lack of arteriographic confirmation of obstructive coronary artery disease (Fulton *et al.*, 1972; Krauss, Hutter, and DeSanctis, 1972; and Gazes *et al.*, 1973). Clinical recognition of these syndromes has assumed increased importance since the demonstration that myocardial infarction is often preceded by premonitory symptoms (Solomon, Edwards, and Killip, 1969; Hochberg, 1971; Nixon and Bethell, 1974). Rapid advances in the technique of coronary artery revascularization have led to the application of this surgical procedure to patients with certain unstable anginal syndromes. The major objectives in these situations are the prevention of acute myocardial infarction and the prolongation of life (Lambert *et al.*, 1971; Favaloro *et al.*, 1971; Vogel *et al.*, 1971; Bolooki *et al.*, 1972; Vogel *et al.*, 1975).

A new myocardial scintigraphic technique, using technetium-99m stannous pyrophosphate, has recently been shown to add another dimension to our ability to recognize acute myocardial infarction in man and in animals (Parkey *et al.*, 1974; Willerson *et al.*, 1975 a, b; Bonte *et al.*, 1974). The application of this new imaging technique to 31 patients with

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unstable angina pectoris, together with a description of the clinical, left ventriculographic, and coronary arteriographic findings, forms the basis for this report.

Methods

The 31 patients studied were admitted to the coronary care unit at Parkland Memorial Hospital, Dallas, Texas. There were 19 men; the age range was 34 to 68 years (mean 52 years). Unstable angina for the purposes of this study was defined as either crescendo angina or acute coronary insufficiency.

Acute coronary insufficiency represented that situation in which a single relatively prolonged episode of chest pain occurred in a patient with a background of stable angina pectoris. Eight patients presented with a history of stable angina in the past and one or more recent episodes of angina lasting more than 30 minutes, simulating acute myocardial infarction. The presenting episode of pain was more severe than previous ones and was not entirely relieved by nitroglycerin.

Twenty-three patients exhibited a crescendo angina pattern. This was defined as a definite and progressive change in the pattern of stable angina without any demonstrable precipitating cause such as increased physical activity, emotional stress, or discontinuance of medical therapy. Specifically, their angina was more frequent, of longer duration, less responsive to nitroglycerin, and occurred with less provocation than previously.

The cardiac rhythm was continuously monitored graphically in the coronary care unit. Standard 12-lead electrocardiograms and serial serum enzyme determinations were performed for at least 3 consecutive days after hospital admission. Myocardial infarction was considered to have been excluded if there were: 1) no rise in serum AST or CK above normal values in the absence of intramuscular injections; 2) no new QRS abnormalities on the electrocardiogram; and 3) nonspecific alterations of the ST segment and T wave that were of transient nature only. A diagnosis of previous myocardial infarction was established in 12 patients by either review of previous records or by the presence of diagnostic Q waves on the electrocardiogram.

All patients had myocardial imaging performed approximately 60 minutes after the intravenous injection of 15 mCi of technetium–99m tagged to 5 mg stannous pyrophosphate (^{99m}Tc-PYP). The technical aspects and historical background of this imaging process have been reported previously from our institution (Parkey *et al.*, 1974; Willerson *et al.*, 1975 a, b). The majority of the myocardial scintigrams were obtained at the patient's bedside using a portable Nuclear Data scintillation camera. Scintigrams were generally obtained within 24 hours of admission and many of the patients had at least one follow-up scintigram 2 to 4 days after admission. The imaging was done in at least three views: anterior, left anterior oblique, and left lateral.

The myocardial scintigrams were graded on a 0 to 4+ scale according to the degree of uptake of the radionuclide over a certain region of the heart, as described previously (Parkey *et al.*, 1974; Willerson *et al.*, 1975 a, b). A negative scintigram is shown in Fig. 1. Acute transmural myocardial infarction presents as an intense, localized area of increased activity (3 to 4+) over the anatomical region of the heart corresponding to electrocardiographic localization of the infarct (Fig. 2) (Parkey *et al.*, 1974; Willerson *et al.*, 1975 a, b). Acute subendocardial infarction, on the other hand, is characterized scintigraphically by faintly positive, diffuse ^{99m}Tc-PYP myocardial uptake (2+) (Fig. 3) which is generally difficult to localize (Willerson *et al.*, 1975 a, b).

Cardiac catheterization with selective coronary arteriography was performed in each of these patients after the completion of the diagnostic studies described above. These studies were done 3 to 14 days after admission and after propranolol had been discontinued for at least 24 hours. Left ventriculography was performed in the right anterior oblique position, and filming was done at 60 frames/s with a 35 mm camera. Left ventricular end-diastolic and end-systolic volumes were determined by the area length method (Kasser and Kennedy, 1969). Left ventricular ejection fraction was calculated as the ratio of stroke volume to end-diastolic volume. Coronary

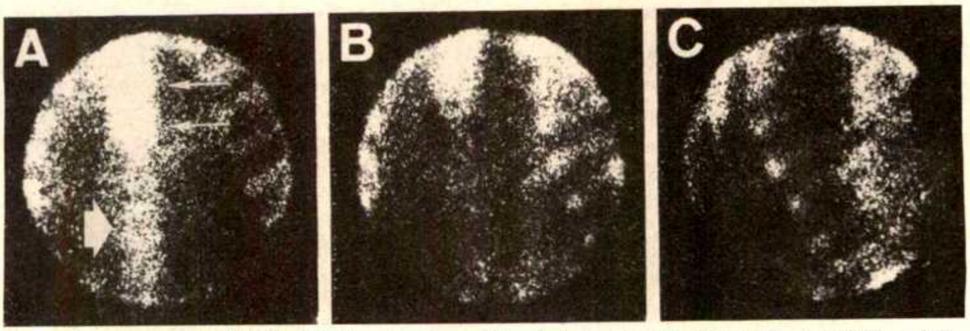

FIG. 1 *A negative ^{99m}Tc-PYP scintigram. Panel A is an anterior view, panel B a left anterior oblique view, and panel C a left lateral view. Note the uptake in the sternum and vertebral column (arrows point to these structures in panel A). Also note the faint uptake of the ^{99m}Tc-PYP in the ribs.*

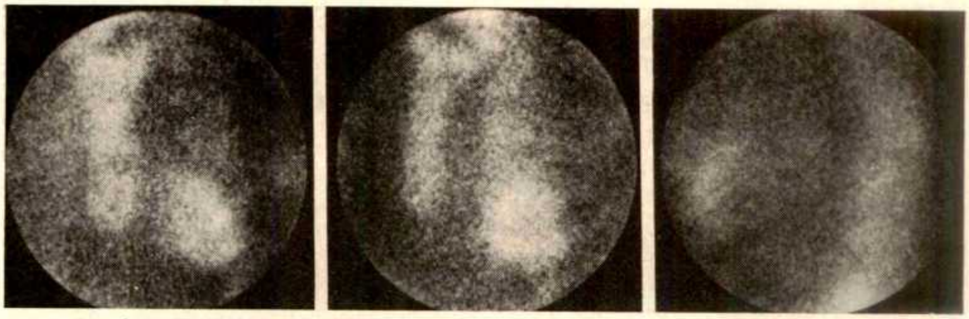

FIG. 2 *A ^{99m}Tc-PYP myocardial scintigram that shows an anterior and apical myocardial infarction. The three views are the same as in the preceding figure. Note the increased uptake of the ^{99m}Tc-PYP in the anterior and apical regions of the heart.*

arteriographic lesions were considered significant if they produced at least a 70 per cent reduction in luminal diameter.

Initial treatment in all patients consisted of sublingual isosorbide dinitrate and oral propranolol hydrochloride as needed for control and prevention of further attacks of ischaemic pain. Every attempt was made to relieve the chest pain in these patients before subjecting them to cardiac catheterization and in nearly every instance this was successful (see 'Results').

Results

The results of the ^{99m}Tc-PYP myocardial imaging in these patients were of interest. Twenty patients had negative ^{99m}Tc-PYP myocardial scintigrams (Table 1). Eleven patients (Table 2) (35% of the entire group) showed faint and diffusely positive uptake of the ^{99m}Tc-PYP in a 2+ positive pattern (Parkey *et al.*, 1974; Willerson *et al.*, 1975 a, b). This pattern (Fig. 4) is similar to that observed in patients with acute subendocardial infarction (Willerson *et al.*, 1975 a, b). However, none of these 11 patients exhibited any of the enzymatic or electrocardiographic criteria indicating the presence of myocardial necrosis.

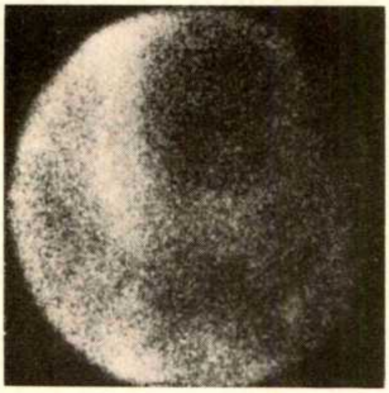

FIG. 3 *A ^{99m}Tc-PYP scintigram obtained in a patient with an acute subendocardial myocardial infarction. Note the characteristic faint and diffuse uptake of the ^{99m}Tc-PYP in this type of infarction.*

The clinical features, coronary arteriographic findings, and left ventricular ejection fractions are detailed in Tables 1 and 2. A comparison of clinical features between these two scintigraphic groups (Table 3) shows an identical mean age, that previous myocardial infarction appeared to be slightly more common in those with negative scintigrams, and that the crescendo pattern of angina and recurrence of angina after the initiation of strict bed-rest tended to be more characteristic of those patients with positive scintigrams. Of interest is the fact that all the patients with positive ^{99m}Tc-PYP scintigrams had crescendo angina except for two who had coronary insufficiency (Tables 1 and 2).

Left ventricular function, as determined by the left ventricular ejection fraction, showed only a tendency (not statistically significant) towards slightly poorer ventricular performance in those patients with positive ^{99m}Tc-PYP myocardial scintigrams. The 2 patients (patients CO and LJ) with the lowest ejection fractions both had positive ^{99m}Tc-PYP myocardial scintigrams (Table 2). Two patients (JM and GW) with positive scintigrams had ventriculographic studies inadequate for volume determinations because of ventricular ectopic beats during angiography (Table 2).

Coronary arteriography was uneventfully performed in all patients; the results are summarized in Tables 1 and 2. Three patients had angiographically normal coronary arteries, an incidence of 10 per cent for the entire group. Each of these 3 patients had a negative myocardial scintigram. Isolated lesions of single coronary arteries were observed in 4 patients, 2 of whom (JM and DD) had disease localized to circumflex marginal vessels in

TABLE 1 *20 patients with unstable angina pectoris and negative ^{99m}Tc-PYP myocardial scintigrams*

Patient	*Age and sex*	*Previous MI*	*Clinical syndrome*	*Angina in CCU*	*EF (%)*	*Sites of stenosis*
LE	49 M	0	CI	0	68	0
ES	34 M	0	CI	0	61	0
CJ	45 F	0	CA	0	58	0
MS	39 F	0	CA	+	58	L
EJ	46 M	+	CA	0	52	L, C
AR	44 F	0	CA	0	65	C, R
DP	62 M	+	CA	0	65	LM, L, C, R
LR	46 F	0	CA	0	64	L, R
DO	52 F	+	CI	+	59	L, C, R
LC	50 F	+	CI	0	63	L, C, R
DF	66 M	0	CA	+	47	LM, C, R
DW	38 M	+	CI	0	61	L, C, R
FC	61 M	+	CA	+	63	L, C, R
JV	35 M	+	CI	0	60	LM, L, C, R
FR	51 M	+	CA	0	45	L, C, R
CB	68 F	0	CA	0	65	LM, L, C, R
AA	62 F	+	CA	0	41	L, C, R
TH	66 M	+	CA	0	41	L, C, R
JB	51 M	0	CA	0	39	LM, L, C, R
CM	58 M	0	CA	0	43	L, C, R

CI, coronary insufficiency; CA, crescendo angina; EF, ejection fraction; L, left anterior descending coronary artery; LM, left main coronary artery; C, circumflex coronary artery; R, right coronary artery.

TABLE 2 *11 patients with unstable angina pectoris and 2+ positive ^{99m}Tc-PYP myocardial scintigrams*

Patient	*Age and sex*	*Previous MI*	*Clinical syndrome*	*Angina in CCU*	*EF (%)*	*Sites of stenosis*
JM	55 M	0	CA	+	*	C
DD	50 F	0	CA	+	57	C
CO	55 M	0	CA	0	22	L, C
LJ	53 M	+	CI	0	26	L, C, R
JW	48 M	0	CA	0	45	L, C, R
BW	56 M	0	CA	+	56	L, C, R
SW	51 M	0	CA	0	59	LM, L, R
EL	61 M	0	CA	+	57	LM, L, C, R
EB	59 M	+	CI	0	39	C, R
GW	37 F	0	CA	+	*	L
CT	53 F	0	CA	+	71	L, C, R

Abbreviations as in Table 1.
*Accurate measurement impossible because of frequent ventricular premature beats during left ventricular angiography.

association with positive ^{99m}Tc-PYP myocardial scintigrams. Triple-vessel involvement was present in 19 patients (61%), with 7 showing significant stenosis of the left main coronary artery before its bifurcation into anterior descending and circumflex branches. Apart from the absence of normal coronary arteriograms in those patients with positive ^{99m}TC-PYP myocardial scintigrams, there were no differences in the distribution of coronary arteriographic abnormalities between the two groups of patients.

The institution of strict bed-rest and the initiation of treatment with sublingual isosorbide dinitrate and propranolol hydrochloride were highly successful in most patients in producing relief of pain. Whereas pain did recur after admission in 10 patients, in only 3 of these was there a poor response to intensive medical therapy. The short-term follow-up in these patients over an average period of 6 months includes 18 patients who received only medical treatment and subsequently had a total of 6 major ischaemic events: 4 deaths and 2 nonfatal myocardial infarctions. None of these 6 events occurred sooner than 2 weeks after admission; 4 occurred in patients unsuitable for surgical intervention because of poor left ventricular function or unsuitable distal vessels for bypass grafts, one of whom was a patient with a 2+ positive ^{99m}Tc-PYP myocardial scintigram. Permission for necropsy was not obtained in this patient. Surgical revas-

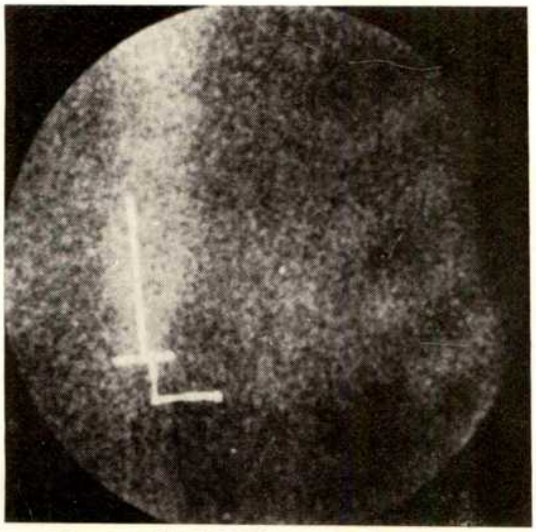

FIG. 4 *A ^{99m}Tc-PYP myocardial scintigram obtained from a patient with unstable angina pectoris. Note the faint and diffuse uptake of the ^{99m}Tc-PYP in a pattern very similar to that shown in the preceding figure in which a subendocardial infarction was present.*

cularization was carried out in 13 patients, including 5 patients with left main coronary artery lesions and 5 patients with 2+ faintly and diffusely positive ^{99m}Tc-PYP myocardial scintigrams. There has been one operative death and one perioperative infarct in the surgical group so far. The operative death occurred in a patient with a negative ^{99m}Tc-PYP scintigram; the perioperative infarct occurred in a patient with a positive scintigram preoperatively; the patient survived.

Discussion

The various surgical, pharmacological, and physiological techniques developed for the treatment of ischaemic heart disease have attained a degree of sophistication whereby their application to patients with unstable angina may have prophylactic value. Therefore, these interventions deserve careful, controlled study in the future (Fowler, 1971). Myocardial scintigraphy may be of assistance in such investigations. The observation that 35 per cent of our unstable angina patients had positive ^{99m}Tc-PYP myocardial scintigrams identical to those seen after acute subendocardial myocardial infarction raises an obvious question. Had these patients already sustained a minor degree of subendocardial necrosis undetectable by standard diagnostic methods or did they have severe ischaemia which was potentially reversible? Experimental studies done at our institution in dogs suggest that the ^{99m}Tc-PYP is accumulated by irreversibly damaged myocardial cells (Buja *et al.*, 1975 a, b); it has not been possible so far to show that ischaemic but non-necrotic cells take up ^{99m}Tc-PYP. The cellular basis for the accumulation of ^{99m}Tc-PYP by infarcted myocardium is thought to be the labelling of calcium which is deposited in crystalline form in and near mitochondria in necrotic cells, but the possibility that polymorphonuclear labelling or even that some other mechanism may play a part has not yet been excluded (Buja *et al.*, 1975 a, b). In experimental animals histological examination of these regions has confirmed the correlation between myocardial necrosis and increased isotope uptake (Botvinick *et al.*, 1975; Stokely *et al.*, 1976). The possibility does exist, however, that the faintly and diffusely positive ^{99m}Tc-PYP myocardial scintigrams obtained in one-third of the patients with unstable angina indicate cells which are severely ischaemic, but not necessarily destined for necrosis. Appropriate follow-up scintigraphic data are not available at this time and it is not possible to comment on evolutionary changes which may occur in the ^{99m}Tc-PYP myocardial scintigrams in these patients spontaneously or after surgical revascularization. Such information might be particularly useful in prospective studies designed to evaluate various surgical and medical interventions in unstable angina. It is also possible, of course, that the positive ^{99m}Tc-PYP myocardial scintigrams are false positives. This seems unlikely to us since with more than 800 patients studied at our institution using this myocardial imaging technique we have no other sizeable patient group without myocardial infarction but with positive ^{99m}Tc-PYP myocardial scintigrams, even though many patients with relatively stable angina pectoris have been studied. Previous investigators have convincingly shown that at necropsy in many patients with coronary artery disease, there may be scattered areas of myocardial necrosis with no corresponding electrocardiographic or enzyme evidence

TABLE 3 *Comparison of clinical and certain cardiac catherization features in patients with and without positive ^{99m}Tc-PYP scintigrams*

	Negative myocardial scintigram (20)	*Positive myocardial scintigram (11)*
Age (yr)	52	52·5
Crescendo angina	14 (70%)	9 (82%)
Previous MI	10 (50%)	2 (18%)
Angina in CCU	4 (20%)	6 (55%)
Ejection fraction	56%	48%

of myocardial infarction during life (Allison *et al.*, 1963; Hudson, 1965; Eliot and Edwards, 1974). Thus, it seems possible that the positive ^{99m}Tc-PYP scintigrams obtained in one-third of our patients with unstable angina pectoris do indeed indicate limited areas of subendocardial necrosis undetected by traditional means of diagnostic evaluation, viz. electrocardiograms and enzymes.

The higher than expected incidence of significant lesions involving the left main coronary artery in our patients is consistent with some other previous observations (Vogel *et al.*, 1975; Conti *et al.*, 1973). However, the patients with left main coronary artery lesions could not be identified on the basis of the ^{99m}Tc-PYP myocardial scintigrams in this study. Also the finding of normal coronary arteriograms in 10 per cent of our patients with unstable angina pectoris is similar to that reported in other series (Conti *et al.*, 1973; Alison *et al.*, 1975; Scanlon *et al.*, 1973; Fischl, Herman, and Gorlin, 1973).

There does appear to be a tendency for patients with positive ^{99m}Tc-PYP myocardial scintigrams not to have a previous history of myocardial infarction but to have a clinical presentation of crescendo angina with continuing chest pain after admission, as compared with those patients with negative scintigrams. A possible explanation is that these patients have larger amounts of viable but yet severely ischaemic myocardium with small islands of cell death.

The best treatment for patients with unstable angina is at present unknown. In some centres these patients are considered virtual surgical emergencies. In a recently published large series of unstable angina, 85 per cent of the patients treated with propranolol were notably improved, allowing for a 'cooling off' period, followed by semi-elective coronary artery bypass surgery (Alison *et al.*, 1975). The fact that no myocardial infarctions or deaths occurred within 2 weeks of admission to hospital in our series suggests further that definitive cardiac catheterization and coronary arteriography can probably be safely postponed for several days after admission especially in those patients who lose their pain with strict bed-rest and appropriate drug treatment.

The brief follow-up period of both medically and surgically treated patients in this study suggests that a 2+ faintly and diffusely positive ^{99m}Tc-PYP scintigram in this setting without other evidence of myocardial infarction is of no immediate prognostic value. Of the 8 severe ischaemic events, 6 occurred in those patients with negative myocardial scintigrams. We do not therefore delay either necessary cardiac catheterization or cardiac surgery when the ^{9m}Tc-PYP myocardial scintigram is 2+ positive in patients with unstable angina who have no electrocardiographic or enzymatic evidence of infarction. On the other hand, we would treat the patient as having a myocardial infarct rather than as unstable angina pectoris, when the ^{99m}Tc-PYP myocardial scintigram is 3–4+ positive, or there is a scintigram that is positive and becomes negative in association with a single prolonged episode of pain suggesting infarction, or a positive scintigram associated with traditional evidence of myocardial infarction.

Any conclusions about the specific role of the ^{99m}Tc-PYP imaging technique in the long-term management of patients with unstable angina would be premature at present. However, it seems probable that at least some if not all of these patients with unstable angina pectoris and 2+ diffusely and faintly positive ^{99m}Tc-PYP myocardial scintigrams have already sustained a small area of subendocardial infarction undetectable by less sensitive diagnostic tests. The ^{99m}Tc-PYP myocardial scintigram should be a valuable aid in future investigations into the natural history of unstable angina, and in the evaluation of other diagnostic methods that will be developed which are capable of detecting very small amounts of myocardial damage. It should also be of help in evaluating therapeutic measures that are designed to interrupt the progression of unstable angina pectoris to myocardial infarction.

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Regression of primary pulmonary hypertension

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A girl who presented in childhood with advanced primary pulmonary hypertension and whose condition later improved is described. This is the first time to our knowledge that documented regression of the disease has been reported.

Idiopathic pulmonary hypertension, including childhood and familial primary pulmonary hypertension, is usually a fatal disease. Wood (1956) reported an average survival of 3·2 years from the onset of symptoms in a series of 20 patients. A few patients live much longer and show relatively long-term stability, but even in these more fortunate cases eventual deterioration and death is still the rule. Nielsen and Fabricius (1961) reported 3 out of 14 patients who were still living 15 to 20 years after the onset of symptoms. Charters and Baker (1970) described a case of primary pulmonary hypertension in a man who died at the age of 25 years, 19 years after the onset of symptoms. In their huge series Wagenvoort and Wagenvoort (1970) recorded 4 out of 110 patients in whom symptoms had been present for between 20 and 29 years before death.

We report here a patient in whom primary pulmonary hypertension regressed after the disorder had reached an advanced stage. We have been unable to find any reports of comparable cases. The only other report of improvement was of a patient whose pulmonary hypertension was thought to be thromboembolic in origin (Wilcken, MacKenzie, and Goodwin, 1960): these authors recorded a drop in pulmonary artery pressure from 65/28 to 40/20 mm Hg (8·6/3·7 to 5·3/2·7 kPa) during anticoagulant treatment.

Case report

The patient was born at term after a normal pregnancy and uncomplicated delivery. Her development was normal and she had had no serious illnesses. There was no relevant family history; the parents and a younger sister were healthy.

She had been apparently quite well until the age of 10 when in May 1966 she fainted momentarily. Between June 1966 and December 1966 she fainted six times, always when running or climbing stairs. Since the onset of the fainting episodes she had also noticed breathlessness on exertion and could not walk at a normal pace on the flat without dyspnoea.

The patient was first seen at Hammersmith Hospital in April 1967 at the age of 11 years and was then overweight (40·4 kg and 145 cm, on the 90th centile for weight and the 50th centile for height), but looked fit. There were no signs of puberty. She was acyanotic and not clubbed. The heart rate and rhythm were normal; the blood pressure was 105/75 mmHg (14·0/10·0 kPa) but she had signs of severe pulmonary hypertension. The jugular venous pressure showed a 6-cm 'a' wave. There was a pronounced right ventricular heave and pulmonary arterial pulsation with a palpable pulmonary component of the second sound. There was a right ventricular fourth sound, a pulmonary ejection click, and a soft, short, ejection systolic murmur. The pulmonary component of the second sound moved normally with respiration and there was no pulmonary regurgitant murmur. The lung fields were clear on auscultation.

Investigations

Haematological and biochemical investigations were all normal. The electroencephalogram showed some generalized disorganization but no localizing features. The electrocardiogram showed severe right ventricular hypertrophy with widespread T wave changes (Fig. 1). The chest radiograph showed slight cardiac enlargement with prominent main pulmonary arteries and clear lung fields with normal or reduced vascularity (Fig. 2a).

Cardiac catheterization had already been carried out elsewhere in January 1967. The results (see Table) confirmed that she had severe pulmonary hypertension without any evidence of structural heart disease.

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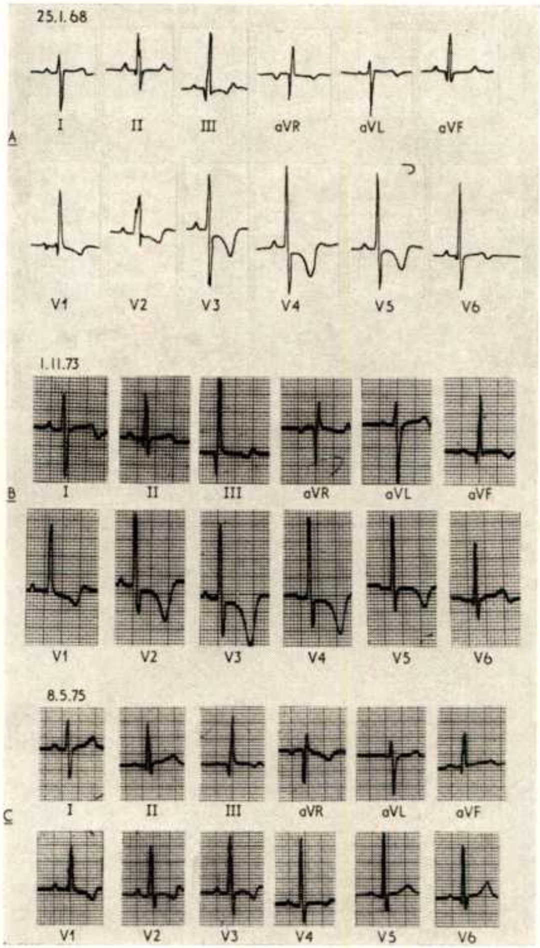

FIG. 1 *Comparison of (A) electrocardiograms recorded in 1968 (when aged 11 years), (B) 1973 (aged 17), and (C) 1975 (aged 19), suggests decrease in severity of right ventricular hypertrophy between 1973 and 1975. (Electrocardiograms all recorded at normal standardization, i.e. 10 mm = 1 mV.)*

The diagnosis of primary pulmonary hypertension was accepted and treatment with oral anticoagulants was started.

Progress

From 1967 to 1969 the patient continued to be breathless and feel faint on exertion. She was readmitted to Hammersmith Hospital in August 1969 because of gradual deterioration after a syncopal attack in July 1969 and considerable decrease in exercise tolerance. Physical findings were similar to those in 1967 except that she was even more obese and an early diastolic murmur in the pulmonary area had appeared. Phonocardiograms recorded at this time are shown in Fig. 3A. The electrocardiogram was unchanged from 1967. Chest *x*-ray examination, however, showed a further increase in heart size. A perfusion lung scan was within normal limits. Right heart catheterization was repeated (Table). A pulmonary angiogram showed normal peripheral pulmonary arteries but dilatation of the main pulmonary arteries. It was thought that pulmonary thromboembolism could be excluded as a cause of her recent deterioration. She was, however, continued on anticoagulants and put on an 800-calorie diet.

The patient continued to have syncopal episodes in 1970 and 1971 and had to limit her activities even further. The early diastolic murmur in the pulmonary area became louder. Then, inexplicably, the slow deterioration was halted and she gradually improved. Her last syncopal episode was in 1971. In retrospect we think that the improvement probably started in 1972, when she was 16. Subjective improvement was first noted at her clinic visit in September 1972. Disappearance of the pulmonary regurgitant murmur and loss of ejection click were noted in May 1973.

In 1973 she left school, and her father bought her a car because of her disability. She learned to drive and drove to and from a sedentary job as a clerk with a travel firm.

By 1975 she had become virtually asymptomatic and now leads a normal, active life. She was readmitted to Hammersmith Hospital for reinvestigation. At 19 she was a fit-looking, well-developed young woman, still slightly obese. The cardiac findings were totally changed. The giant venous 'a' wave in the neck, the pulmonary ejection click, and the murmur of pulmonary regurgitation had all disappeared. The right ventricular heave and the palpable pulmonary closure sound were less prominent. The phonocardiogram (Fig. 3B) showed only a soft systolic murmur, with a prominent pulmonary component of the second sound, but no ejection click or early diastolic murmur. The electrocardiogram had changed considerably, with reduction in voltage of the R waves in the right praecordial leads and improvement in the previously widespread, steeply inverted T waves (Fig. 1). The chest *x*-ray picture had changed. The steadily enlarging heart seen in films taken between 1967 and 1971 (Fig. 2) was reduced to normal size. Cardiac catheterization was repeated (Table). The pulmonary angiogram was unchanged and still showed dilated main pulmonary arteries with normal peripheral arteries without obstruction. Ventilation and perfusion lung scans showed no significant abnormality. The echocardiogram showed that the movement of the interventricular septum was normal.

Haemodynamic data (Table)

Between 1967 and 1969 the pulmonary arterial pressure was recorded three times and was at or near systemic level at rest on each occasion. Because of her parlous state and the possible risks involved no exercise tests were performed. There was no fall in the pulmonary arterial pressure with administration of 100 per cent

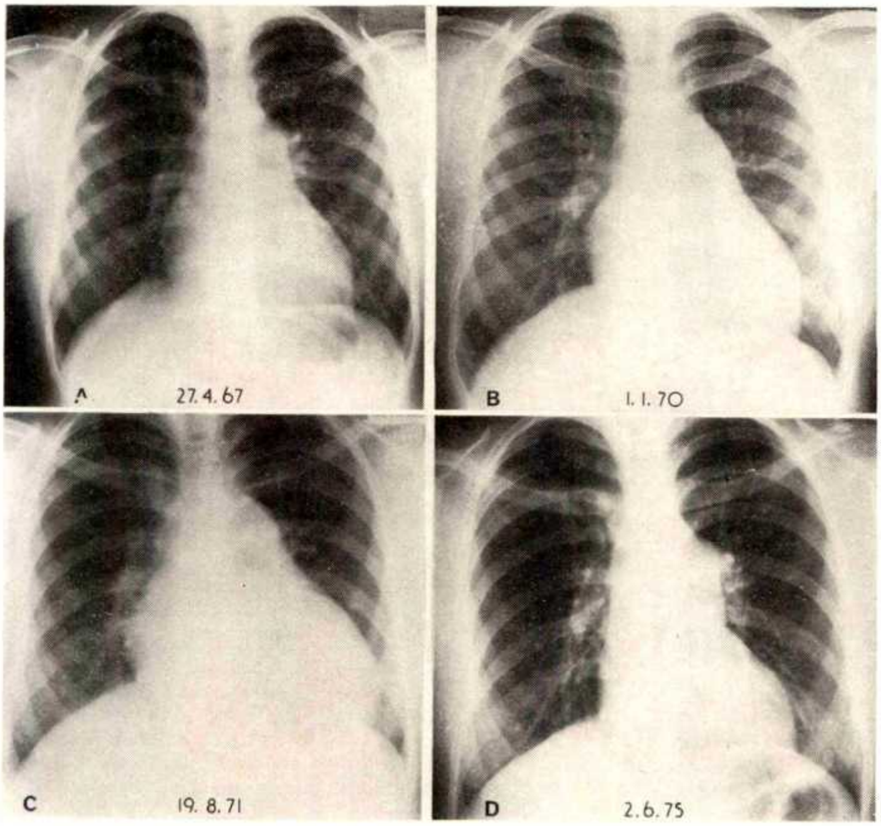

FIG. 2 *Chest* x-*rays taken in 1967, 1970, 1971, and 1975 show a progressive increase in heart size from 1967 to 1971 (Fig. A, B, C) with a pronounced decrease in D.*

oxygen. Bicycle ergometry in 1969 showed that her maximum work load was only 200 kpm/minute. She was then stopped by dyspnoea with a pulse rate of 150/min. The transseptal left heart catheterization carried out in 1967 excluded any abnormality in the left heart chambers or septal defect.

At her fourth study in 1975 the pulmonary artery pressure had fallen to just above normal with a normal systemic pressure and the previously very reduced cardiac output had risen to low normal limits. Bicycle ergometry showed that her exercise performance was now within normal limits (Fig. 4). Lung function is now normal apart from low CO transfer which is 19·3 (predicted 25·7 to 32·9 ml/min per mmHg) consistent with a slight loss of pulmonary vascular bed.

The evidence of true regression of her pulmonary vascular disease was considered to be irrefutable, though it was too early to conclude that she was 'normal' as 'cured'.

Discussion

This case of apparent improvement from a presenting severe state of primary pulmonary hypertension raises a number of points worthy of discussion, particularly in relation to the possible causes or the mechanism of raised pulmonary vascular resistance.

The diagnosis of primary pulmonary hypertension is made only after exclusion of identifiable causes of pulmonary hypertension—in particular, postcapillary pulmonary hypertension caused by mitral valve disease or left heart failure, and precapillary pulmonary hypertension caused by congenital septal defects with the Eisenmenger reaction. Pulmonary thromboembolism or primary lung disease also need to be eliminated. In our patient organic heart disease had been excluded and there was no evidence of primary lung disease. Pulmonary thromboembolism was a theoretical possibility but was most unlikely in a girl of 11, and was excluded by the normal pulmonary angiogram and lung scan in 1969 (Wilson *et al.*, 1973). The lack of respiratory illness or haemoptyses, repeatedly clear lung fields on *x*-ray examination, and normal

TABLE *Cardiac catheterization data recorded in 1967 (2 procedures), 1969 and 1975*

	SVC	*IVC*	*RA*	*RV*	*PA*	*PV*	*LA*	*LV*	*SA*	*SA (100% O_2)*	*CI*	*TPR*
1967 (a)											—	—
Pressures (mmHg)	—	—	M 7·5	—	76/40	—	—	—	100/70	—		
O_2 saturation (%)	74	71	68	67	67	—	—	—	89	99		
1967 (b)											—	—
Pressures (mmHg)	—	—	M 5	96/8	100/60 M 80		M 7	106/8	120/75	—		
O_2 saturation (%)	—	—	—	—	62	90	94	93	87	—		
1969											1·5	17·0
Pressures (mmHg)	—	—	M 10	95/12	95/39 M 58	—	—	—	100/70*	—		
O_2 saturation (%)	—	—	—	—	64	—	—	—	97	—		
1975											2·3	3·8
Pressures (mmHg)	—	—	M 2	40/4	40/14 M 24	—	—	—	110/70	—		
O_2 saturation (%)	—	—	—	—	66	—	—	—	97			

*Sphygmomanometer cuff measurement. RA=right atrium; RV=right ventricle; PA=pulmonary artery; SA=systemic artery; LA=left atrium; LV=left ventricle; IVC=inferior vena cava; SVC=superior vena cava; PV=pulmonary vein; M=mean; 100% O_2 indicates administration of 100% O_2 at time of sampling; CI=cardiac index in l/min per m^2; TPR=total pulmonary resistance in units/m^2.

Conversion from Traditional units to SI units: 1 mmHg≈0·133 kPa.

lung scans made pulmonary venous obstruction (as in pulmonary veno-occlusive disease) extremely unlikely in our patient.

It is unlikely that the anticoagulants were directly relevant to the patient's recovery or that the association between treatment and improvement points to a thromboembolic origin of the pulmonary hypertension. It was hoped that anticoagulation would prevent pulmonary arterial thrombosis of thromboembolism as a secondary complication of the advanced stages of the disorder and that it might, therefore, prolong life (Wagenvoort and Wagenvoort, 1970). This is disputed by Walcott, Burchell, and Brown (1970) who noted in a retrospective study of 23 patients with primary pulmonary hypertension that anticoagulation did not appear to alter the natural history of the disease or the survival time. In the absence of specific therapy for this disease of undetermined aetiology, however, we believe that oral anticoagulants should be prescribed in idiopathic pulmonary hypertension and continued indefinitely.

Primary pulmonary hypertension is commonest in young women—usually in those who have been pregnant. In childhood, girls and boys are equally affected; the disorder is sometimes familial, and it may occur in sibs. The nature of the underlying disease process is still undetermined. Though a congenital abnormality in the pulmonary arterial wall remains a possibility, Heath and Edwards (1960), Roberts (1963), and Wagenvoort and Wagenvoort (1970) showed that in most patients (including children) the pulmonary hypertension was not apparently present from birth but was acquired. Subramanian *et al.* (1974) found the 'adult' pattern of fragmented elastic fibres in the wall of the main pulmonary arteries in all of their 11 cases. This observation indicated that the disease had been acquired after a postnatal and childhood interval of low pulmonary artery pressure even in the 6 of their patients who died before the age of 16.

A family predisposition to the development of the disease in childhood sheds no light on aetiology, but these cases sometimes survive for a relatively long time (Fleming, 1960; Melmon and Braunwald, 1963). Wagenvoort and Wagenvoort (1970) described 11 such familial cases and from the published reports collected 47 other cases from 20 different families. There was no family history associated with our patient.

Farrar (1963) and Wade and Atukorale (1975) have contended that the disease is part of an autoimmune process. This is supported by the association of pulmonary hypertension with rheumatoid and other collagen diseases as well as with Raynaud's phenomenon as described by Walcott *et al.* (1970) and by Wagenvoort and Wagenvoort (1970). Both of Trell's cases (1973) of primary pulmonary hypertension with an unusually long duration had Raynaud's phenomenon. There was no evidence of

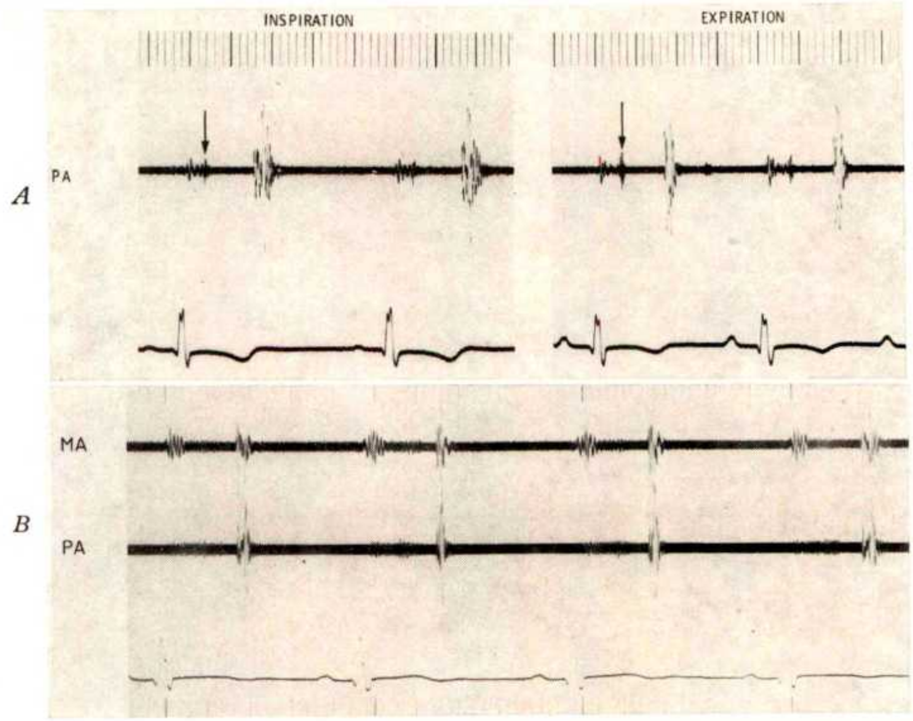

FIG. 3 *Phonocardiograms recorded in 1969 (A) show loud pulmonary component of second sound which moves normally with respiration, and an ejection click (arrowed). Early diastolic murmur, then clinically prominent, does not show clearly. Phonocardiogram in 1975 (B) shows only soft systolic murmur. The ejection click has gone. The pulmonary component of second sound still appears to be loud. MA=mitral area. PA=pulmonary area.*

collagen vascular disease in the patient described here. Farrar also noted that in some cases the onset of the disease seemed to be preceded by a virus-like illness, and this association was also mentioned by Walcott and his colleagues (1970). Again there was no history of such an illness in our patient before the onset of her symptoms.

The use of the anorectic drug aminorex fumarate (Menocil) has been implicated in some cases of pulmonary hypertension but there was no history of the use of this drug or of other 'slimming' drugs in our patient whose disease started some years before she had any interest in slimming.

Wood (1952) was probably the first to suggest that pulmonary hypertension might be vasoconstrictive in origin and a self-perpetuating response to some initiating degree of pulmonary hypertension itself. Evans, Short, and Bedford (1957), and Wade and Ball (1957) supported this view and Short (1959) cited earlier physiological work which showed that, like smooth muscle in other situations, the vascular coats of arteries react to a stretching force by constriction. Wood (1959) found that patients with primary pulmonary hypertension responded to injection of acetylcholine into the pulmonary artery by a brisk fall in pulmonary artery pressure, and this seemed to support the concept of vasoconstriction. The pathological work of Wagenvoort and Wagenvoort (1970) led them to support a vasoconstrictive pathogenesis and to reintroduce Wood's term 'vasoconstrictive pulmonary hypertension' to describe this group with primary pulmonary hypertension. The notion that there exists an individual susceptibility or hyperreactivity of the muscular pulmonary arterioles in patients who develop pulmonary hypertension in response to the various stimuli that may trigger pulmonary vasoconstriction is all that is known about causation. Such stimuli may include a high pulmonary artery pressure and pulse pressure associated with intracardiac shunts, increased flow, polycythaemia, hypoxia, and possibly also sexual maturation in the female and

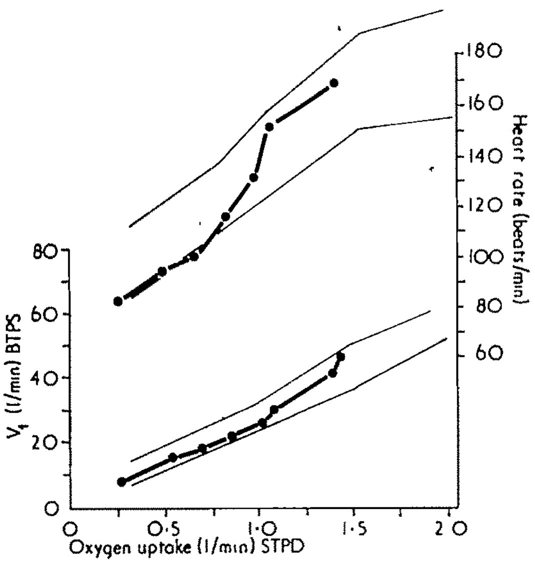

FIG. 4 *Result of progressive exercise test in 1975. Increments in heart rate (above) and ventilation (below) fell within expected normal range (fine lines) for increase in oxygen uptake achieved.*

pregnancy. Reversal of such a postulated vicious spiral could possibly explain the recovery in our patient.

A higher pulmonary artery pressure than normal is found in most dwellers at high altitude than in those who live at sea level. This is normally asymptomatic and benign (Grover *et al.*, 1966). The same authors described the reversal of unusually severe asymptomatic pulmonary hypertension in a patient who had lived at high altitude but moved to sea level, and attributed this to relief from the hypoxic stimulus to pulmonary vasoconstriction that had been present at altitude. It may be of significance that the apparent deterioration in our patient's condition in 1969 occurred after a visit to Switzerland.

The later symptomatic and objective improvement described coincided with a late menarche at the age of 15. This is surprising in the light of the prevalence of idiopathic pulmonary hypertension in adult women and of its relatively common occurrence after pregnancy in contrast to the relative rarity and equal sex ratio in children.

Pregnancy is a serious hazard in pulmonary hypertension. These patients are advised to avoid pregnancy and it is our practice to carry out tubal ligation. Though tubal ligation had originally been planned for our patient and the original advice to avoid pregnancy has been upheld, we no longer feel justified in recommending sterilization. The case is without parallel in our experience, but provided her improvement is maintained over the next few years then it may even be reasonable for her to consider pregnancy, though we feel uneasy about the risk of pregnancy then provoking a recrudescence of her disease.

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Echoventriculography in acute myocardial infarction

II: Monitoring of left ventricular performance

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In acute myocardial infarction the overall left ventricular pump function and the regional performance of the infarcted and non-infarcted myocardial segments were studied serially by echocardiographic techniques in 24 patients during the first week of their illness.

Left ventricular cavity sizes were acutely increased in 62 per cent of the patients ($P<0{\cdot}005$). The end-systolic diameter in anterior infarcts increased to the greatest extent, +44 per cent, the end-diastolic diameter by +27 per cent, giving a volume of 246 ± 25 ml. In the anterior myocardial infarcts all the function parameters deteriorated more than in the posteroinferior ones. Ejection fraction was subnormal ($P<0{\cdot}005$) in every patient, and mean circumferential fibre shortening (Vcf) was slowed by about 30 per cent ($P<0{\cdot}005$).

Regionally, contraction of the infarcted area of the ventricle was asynergic in every instance, and its function was almost totally lost ($P<0{\cdot}001$). Systolic paradoxical motion was a constant and stable finding in the anterior infarctions but not so in the posterior ones. While this asynergic systolic contraction may distort echocardiographic measurement of the end-systolic left ventricular volumes, it certainly does not operate at the end-diastolic phase. The serial deviations from normal in the amplitude or velocity of the uninvolved segments were small, but in the case of clearly enlarged end-diastolic volumes these figures in fact indicate supernormal, compensating function. Both overall and regional performance were worst within the first 3 days of infarction, improving thereafter. The patient with a fatal course showed, instead, progressive deterioration.

This noninvasive left ventriculogram by ultrasound gives valuable insight into overall pump function and ventricular volumes, little studied so far in acute infarction, and it may serially quantify the segmental function of both the infarcted and uninvolved regions.

Modern evaluation and management of acute myocardial infarction is increasingly using techniques that allow a quantitative assessment of the left ventricular function. Left ventricular dysfunction certainly is present in most of these patients, more often than is usually recognized from its subtle signs. Since acute infarction may produce a wide range of physiological disturbances, their correct identification and assessment aids in guiding therapy appropriately to prevent development of more serious cardiac failure and to preserve the still ischaemic, but not yet infarcted, myocardium.

Pressure-flow monitoring is now feasible in coronary care units with relatively simple and convenient techniques (Swan *et al.*, 1970). However quantitative assessment of left ventricular volumes, though fundamentally involved with the overall cardiac function, has not yet become established in the acute phase of infarction, as these measurements are usually based on angiographic techniques. We report here our experience in monitoring serially the dimensions of the left ventricle by using quantitative echocardiography in 24 patients with acute myocardial infarction during the first week of their illness. These data were also related to the serial changes found in the regional contraction patterns which were obtained from both the infarcted and noninfarcted left ventricular segments.

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Subjects and methods

Twenty-four patients, 20 men and 4 women, with acute myocardial infarction, were studied. They make up that portion of 30 consecutive patients reported earlier (Heikkilä and Nieminen, 1975) from whom complete serial observations are available. The age range was from 30 to 64 years. The infarction studied was the first one in all the subjects; in 8 patients it was anteriorly and in 16 posteroinferiorly located. The course was uncomplicated in 8 patients, 12 had moderate left heart failure and 4 serious pulmonary oedema and/or shock. All the patients were treated in the intensive care unit.

The ultrasound study on left ventricular function was performed serially on the 1st, 2nd, 3rd, and 7th day from the onset of symptoms with the Picker Echoview II equipment. An echocardiographic technique developed for detailed scanning of the left ventricle ('echoventriculography') was used for evaluation of both the overall and the regional left ventricular function (Heikkilä and Nieminen, 1975; Nieminen, 1975). The various left ventricular regions are recorded by this method using 4 principal ultrasound beam axis directions; several additional sites may be used according to the enlargement of the left ventricle.

The left ventricular end-diastolic and end-systolic diameters were measured in a standard manner (Feigenbaum, 1972) from axis 1 in our echoventriculographic method (Heikkilä and Nieminen, 1975; Nieminen, 1975). Special care was paid to obtain the true transverse axis of the left ventricle, perpendicular to its estimated long axis. The cubed internal diameters were used to calculate left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes (Pombo *et al.*, 1971). Double determinations were used for all measurements. Stroke volume and ejection fraction (EF) were derived from these: EF=(LVEDV—LVESV)/LVEDV. Circumferential fibre shortening velocity (Vcf) was modified and measured from the echogram as reported earlier (Nieminen, 1975). The latter study, which described left ventricular overall and segmental functions in 43 healthy subjects, served as normal material for calculations of the statistical significances.

Regional wall motion was measured by the amplitude and the mean velocity of the systolic inward excursion of the particular left ventricular endocardial region under study. These local data were successfully obtained in every serial study from each region of the left ventricle, except for a few early patients in whom the lowest inferior region was not at first systematically scanned (Heikkilä and Nieminen, 1975). The function of at least 8 segments is determined from the basic 4 beam directions, i.e. from the upper and lower halves of the septal, anterior, lateral, and posteroinferior left ventricle segments, with additional detailed recordings from possibly other infarcted regions (see Fig. 9). In addition to their systolic amplitude and velocity, asynergic motion abnormalities were analysed by their area, class (grades: normal, hypokinesia: less than 50% of normal motion, akinesia, and paradoxical motion), and extent, the last combining the changes in area and class together.

Results

Overall left ventricular pump function during first week of infarction

Left ventricular end-diastolic and end-systolic internal transverse diameters, ejection fraction, and modified Vcf for days 1, 2, 3, and 7 after the onset of infarction are displayed in Fig. 1, 2, and 3. Left ventricular internal diameters and volumes were above normal values, $P < 0.005$ for each day. End-systolic diameters ranged from 34 to 60 mm; 62 per cent were above 47 mm (normal mean+2 SD), and 86 per cent over about 42 mm (normal mean +1 SD) and the end-diastolic ones ranged from 42

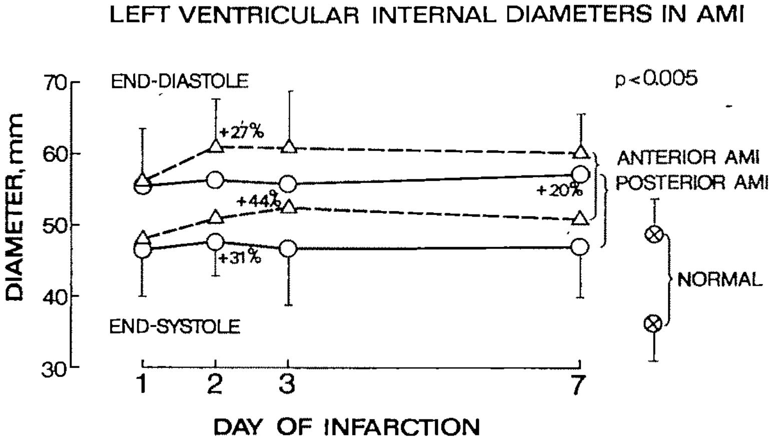

FIG. 1 *Serial changes in mean left ventricular end-diastolic and end-systolic internal transverse diameters shown by echocardiography in acute myocardial infarction. Both are much larger than normal ($P < 0.005$), the end-systolic one more so, and in anterior infarctions more than in posteroinferior ones.*

to 72 mm; 62 per cent over 58 mm (normal mean + 2 SD), and 76 per cent over 53 mm or normal mean +1 SD. In anterior infarctions this cardiac dilatation was most distinct, the mean end-diastolic cavity diameter increased by 27 per cent (61·1±6·5 mm), and the end-systolic one by 44 per cent (52·9±7·0 mm) on day 2. In posterior infarctions, the end-diastolic diameter was most increased by 20 per cent (57·5±7·9 mm) on the 7th day, and the end-systolic one by 31 per cent (47·9±7·1 mm) on the 2nd day. Expressed as end-diastolic volumes, where the cube function of the transverse dimension may be applied with an acceptable accuracy, the left ventricular size in the anterior infarction was 246±25 ml (+106%) and in the posterior ones 208±92 ml (+78%); in the total series, in 75% of the patients it was over 170 ml (normal mean +2 SD).

Stroke volumes calculated from the echograms were lowest on the 1st day in anterior infarctions (76±26 ml) and on the 3rd day in posterior infarctions (73±25 ml), the range being from 11 to 127 ml. These values did not differ significantly from normal (62·0±14 ml).

Ejection fraction remained below 50% in all the acutely infarcted hearts. The lowest figures occurred on the 2nd day in anterior (32±17%) and posterior infarctions (39±12%), $P < 0{\cdot}005$ for both. These values improved thereafter but remained subnormal during the whole observation period.

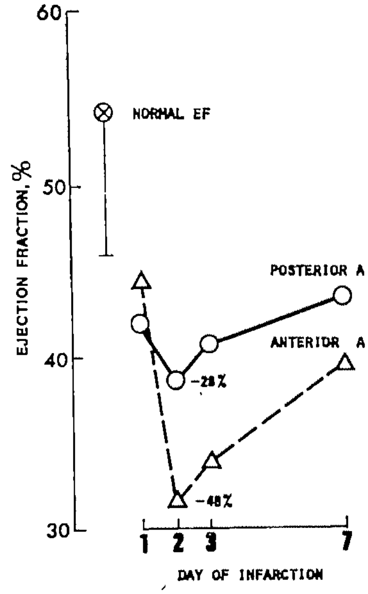

FIG. 2 *Ejection fractions were uniformly reduced in both anterior and posteroinferior acute myocardial infarctions when assessed by echocardiography.*

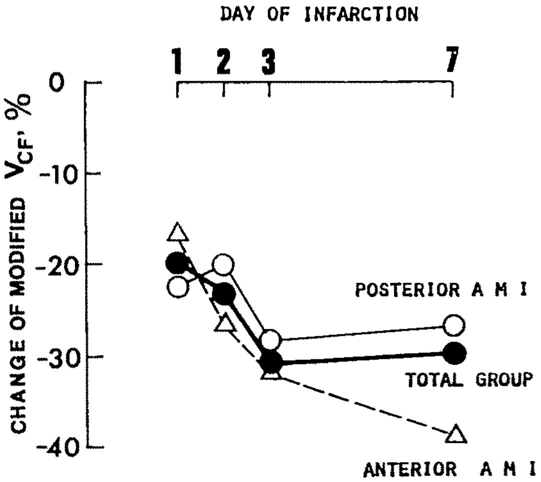

FIG. 3 *Serial changes in modified circumferential fibre shortening velocity (Vcf). About 30 per cent slowing occurs during the first week of acute myocardial infarction.*

Vcf worsened from the 1st ($P < 0{\cdot}05$) to 3rd day ($P < 0{\cdot}005$) similarly in anterior and posterior infarction. It was less than 0·32 (mean –2 SD) in 17 per cent, and less than 0·48 (mean –1 SD) in 92 per cent. In anterior ones Vcf continued to decrease further with time, reaching its lowest figure on the 7th day (–38%, 0·40±0·08 circ/s; normal value 0·64±0·16 circ/s), at which time only it differed from the posterior infarctions ($P < 0{\cdot}05$). In posterior infarctions Vcf did not decrease any further after the 3rd day (–27% to –24%, 0·46±0·07). In contrast to the tendency of ventricular function to improve after the initial days, it deteriorated continuously in the patient who died in hospital.

Sequential changes in regional left ventricular asynergy

Abnormal motion of the infarcted area developed in every patient. The time of maximum asynergic wall motion was the 1st day in 8 patients, 2nd day in 5, and 3rd day in 11, but no later in any of the 24 patients. Serial mean values characterizing abnormal motion of the infarcted left ventricular regions and of the uninvolved segments are displayed in Fig. 4 and 5.

A striking difference exists between anterior and posterior acute myocardial infarctions in regard to segmental function. In anterior infarctions the damaged segment always moved paradoxically and this motion progressed early to its maximum extent, in the majority of patients on the 1st day (in 6 of the 8 patients, and in the other 2 on the following

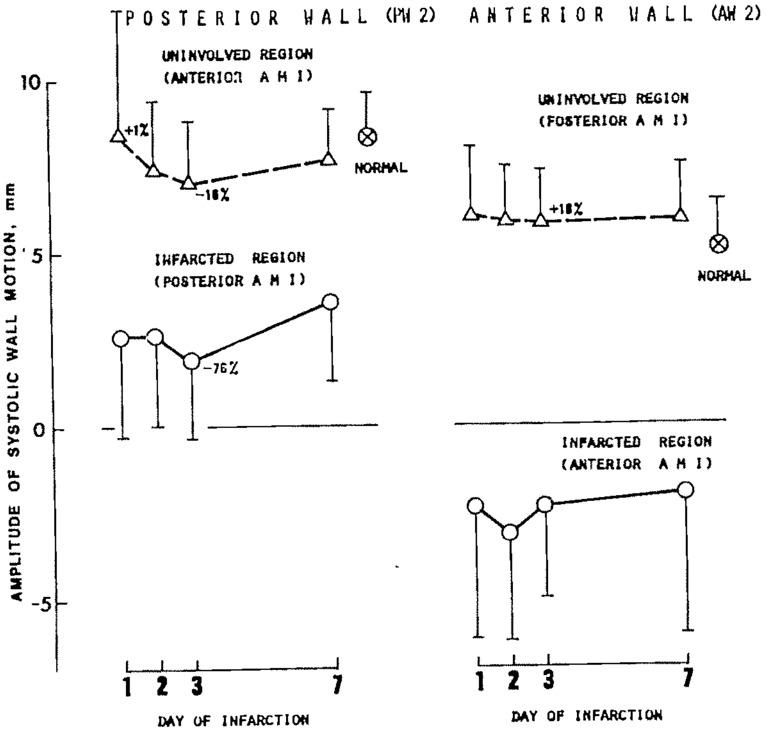

FIG. 4 *Amplitudes of systolic wall motion in infarcted and uninvolved myocardial segments. While motion of the infarcted areas are significantly reduced, or even paradoxical, that of the noninfarcted regions remain mainly within normal ranges. Positive values indicate systolic inward movement and negative values outward movement.*

day) and then remained largely unchanged for a week. The mean amplitude of the systolic outward pulsation was 3·2±3·0 mm. In the posterior infarctions a paradoxical pulsation was an exception; nevertheless, a remarkable reduction of wall motion always occurred in the posterior infarcted areas too (Fig. 6). The asynergic changes of the posterior wall developed more slowly: the maximum was seen on the 1st day in 2 patients, on the 2nd day in 5, and on the 3rd day in 9 of the 16 patients with posterior infarctions. When the maximum abnormality was reached on the 3rd day, the mean amplitude of the asynergic wall motion was only 1·9±2·3mm ($P < 0{\cdot}001$) and the mean velocity 5·2±7·3 mm/s ($P < 0{\cdot}001$), i.e. a reduction by 76 per cent and 84 per cent below the normal, respectively. Thereafter the systolic motion at the infarcted posterior regions slightly improved.

The amplitude of the asynergically moving areas was described serially also as increasing, decreasing, or unchanged by comparing the findings between the beginning and the end of the first week. No clear pattern emerged: in 7 patients the contraction disorder improved, in 9 it remained unchanged, and in 8 the abnormality became worse. However, a difference between anterior and posterior infarctions was again seen. The changes took place mainly in the posterior infarction cases: 6 of the 9 with unaltered amplitude were anterior infarctions, and there were only 2 anterior ones that showed any change: worsening of the paradoxical pulsation after the 1st day.

When serial changes in the qualitative classification of the asynergic motion were studied using the classes paradoxical bulge, akinesia, hypokinesia, or normal motion, no shift from the initial mode was seen in the majority of patients, i.e. in 19 of the 24. In the other 5 the class improved, these had a posterior infarction. Thus the class never worsened in the course of the first week of infarction in either the posterior or the anterior ones. The latter in fact were all already initially in the paradoxical, i.e. the poorest, class.

The extent of the asynergy involving those areas of the left ventricle which showed motion abnormalities was also determined as follows. The abnormality of motion was calculated from 4 anterior (AW1, AW2, AW3, AW4) and 3 posterior (PW1, PW2, PW3, Heikkilä and Nieminen, 1975; Nieminen,

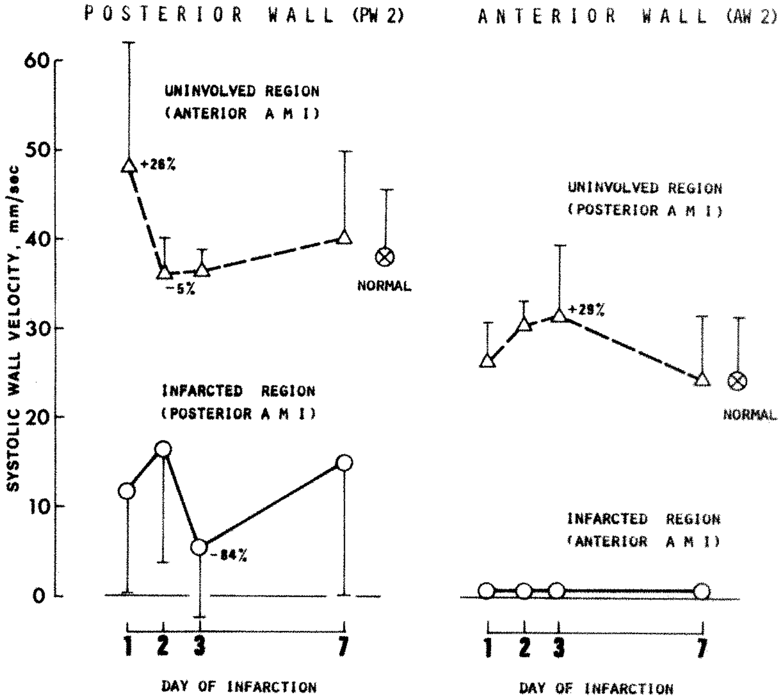

FIG. 5 *Systolic wall velocities in infarcted and uninvolved myocardial segments. Because the anterior infarcted segments always moved paradoxically, their systolic velocities are marked as zero. In posteroinferior infarctions the greatest depression of systolic velocity is seen on the 3rd day, with almost total loss of contraction. On the same day the motion of the noninfarcted anterior wall is most active.*

1975) regions (see Fig. 9) using both the number of sites showing abnormal motion and the shift of the class of asynergy. This index of asynergic motion decreased in 14 of the 24 patients between the 2nd or 3rd and the 7th day. In 10 of these 14 patients the infarct was a posterior one. In only 2 posterior infarcts was an increase of this asynergy observed, and thus in 4 posterior and 4 anterior infarction asynergy remained unchanged.

Function of uninvolved regions

The amplitude and velocity of the systolic contraction in the left ventricular noninfarcted regions remained mainly within the normal ranges in both the anterior and posterior infarctions (Fig. 4 and 5). In the anterior infarctions the greatest motility of the healthy posterior myocardium was seen during the 1st day, the velocity being increased by +26 per cent (48·3±13·9 mm/s; $P < 0·02$) and the amplitude by +1 per cent (8·4±3·8 mm; NS). These values then fell below normal by the 3rd day, –5 per cent, 36·0±4·3 mm/s (NS) and –16 per cent, 7·0±1·8 mm (NS), respectively, to improve slightly thereafter. In posterior infarctions the amplitude of the healthy anterior wall remained serially stable at the high normal range (+18%, 5·8±1·5 mm; NS) while its velocity rose transiently by +29 per cent (31·7±8·6 mm/s, NS) on the 2nd and 3rd days (Fig. 4, 5, and 6).

Development of electrocardiographic abnormalities of infarction in relation to asynergy

Since the electrocardiographic abnormalities in acute myocardial infarction often develop gradually, and since in this echo study the same was seen to be the case with segmental wall motility too, both were analysed together. Of the 8 anterior infarcts, 6 already showed the most severe grade of asynergy during the 1st day. At this time, however, 4 patients had only ST-T changes of injury in the electrocardiogram and did not develop fresh Q waves until the next day. In the 4 other patients with anterior infarction the already initially present Q waves remained unchanged.

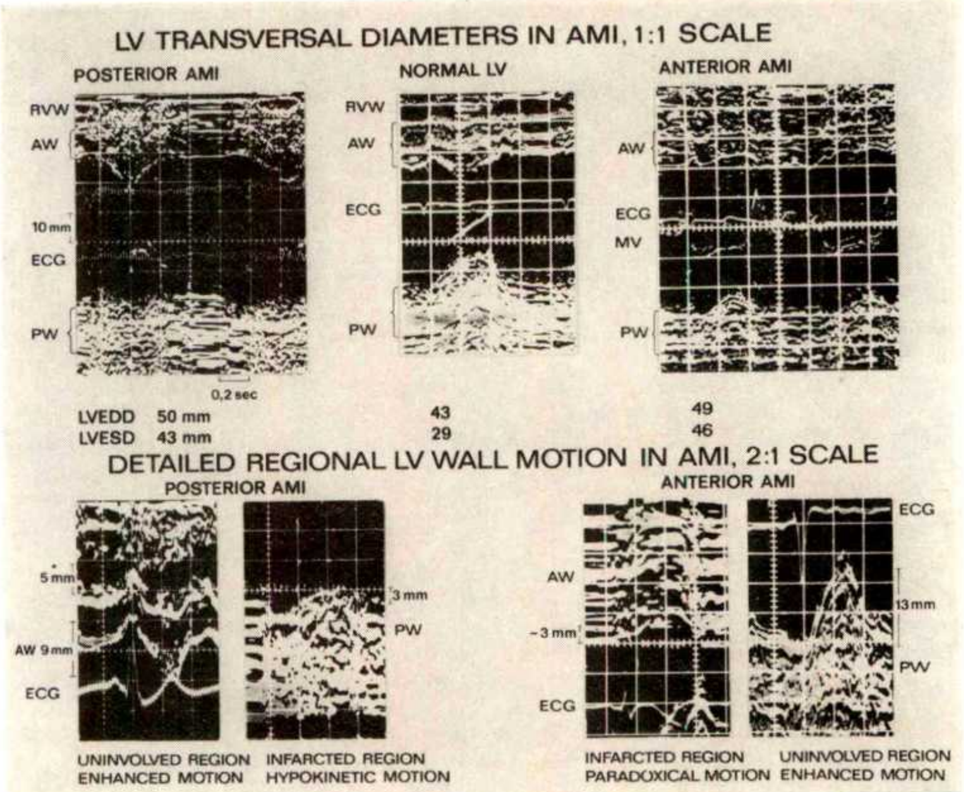
LV TRANSVERSAL DIAMETERS IN AMI, 1:1 SCALE
POSTERIOR AMI
NORMAL LV
ANTERIOR AMI
RVW
AW
10 mm
ECG
PW
0,2 sec
RVW
AW
ECG
PW
AW
ECG
MV
PW
LVEDD 50 mm
LVESD 43 mm
43
29
49
46
DETAILED REGIONAL LV WALL MOTION IN AMI, 2:1 SCALE
POSTERIOR AMI
5 mm
AW 9 mm
ECG
3 mm
PW
UNINVOLVED REGION ENHANCED MOTION
INFARCTED REGION HYPOKINETIC MOTION
ANTERIOR AMI
AW
−3 mm
ECG
ECG
13 mm
PW
INFARCTED REGION PARADOXICAL MOTION
UNINVOLVED REGION ENHANCED MOTION

FIG. 6 *Left ventricular chamber sizes and regional wall motions seen in echocardiography in posteroinferior and anterior acute myocardial infarction. The uninvolved segments were selected for this panel to show the enhanced function which was frequently seen on the first day. The asynergy in anterior infarctions is characteristically a paradoxial pulsation, while in posteroinferior infarctions hypo- or akinetic modes prevail. (AMI = acute myocardial infarction, AW = anteroseptal wall, ECG = electrocardiogram, LV = left ventricle, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, MV = mitral valve, PW = posterior wall of LV, RVW = right ventricular wall.)*

In the cases of posterior infarctions 15 echo-electrocardiogram comparisons were available. Asynergic motion at the infarcted area deteriorated slightly in 12 patients during the first 3 days, and worsening was also noted in 6 of these patients electrocardiographically. Initial ST-T changes alone progressed to fresh large Q waves in 4 of these 6, and in 2 the Q waves deepened only. In 5 patients with posterior infarction the infarction electrocardiogram remained unchanged, and in 1 it improved.

Discussion

The following findings emerged from this serial study on left ventricular function by echocardiography. 1) Remarkable alterations take place in both the overall and the segmental left ventricular performance during the first week of acute myocardial infarction. 2) The echocardiographic picture seen in the anterior acute myocardial infarctions clearly differs from that of the posterior ones (Fig. 7). 3) Asynergic contraction of the left ventricle was documented in all patients with acute infarction by echo left ventriculograms. Such nonuniform contraction may make the volumetric estimations of left ventricular function partially unsatisfactory, so that the ellipsoid approximation may lead to erroneously large, or small, ventricular volume at end-systole. 4) Echo was frequently able to detect distinct abnormalities of ventricular contraction at the time when electrocardiographic changes were still in their initial stage.

Overall left ventricular performance by echo in acute infarction

Left ventricular performance is in a complex way integrated with diastolic ventricular size and pressure (preload), systolic size and pressure (afterload), inotropic state, heart rate, and, especially in ischaemic heart disease, synergy of contraction (Braunwald, 1971). However, in the clinical setting of acute myocardial infarction, only recently have radionuclide cardioangiography and ultrasound provided a means to visualize the heart cavities using a noninvasive technique, with a reasonable quantitative accuracy (Feigenbaum, 1972; Gibson, 1973; Quinones, Gaasch, and Alexander, 1974; Ratshin, Rackley, and Russell, 1974).

Echocardiography in the present study documented various abnormalities in left ventricular function in 100 per cent of the patients, and in the majority of patients (75%) the left ventricular end-diastolic size was significantly enlarged. These findings then confirm the invariable presence of the left ventricular dysfunction which has been found in clinical and haemodynamic studies of the acute phase of infarction (Hamosh and Cohn, 1971; Heikkilä, Luomanmäki, and Pyörälä, 1971a; Gunnar, Loeb, and Rahimtoola, 1974).

The greatest abnormality in the pump function occurred in the end-systolic size and asynergic contraction of the left ventricle. This is obviously the result of the inherent pathophysiological alteration of the infarction: the regional loss of contractile element function (Swan *et al.*, 1972). The great significance of the systolic distortion in the asynergic segments in further stealing pump performance has been convincingly shown by Parmley *et al.* (1973). The contractile force of the uninvolved segments is largely dissipated in generating tension so that inadequate capacity is left for the ejection of blood from the ventricle. The present figures also indicate that asynergic infarcted zones mainly exceeded the critical size of 25 to 30 per cent of the left ventricle, because the size of asynergy correlates well both with the end-diastolic volume and with the ejection fraction (Herman and Gorlin, 1969; Feild *et al.*, 1972; Hamilton, Murray, and Kennedy, 1972; Kitamura *et al.*, 1973; Parmley *et al.*, 1973; Rigo *et al.*, 1974). The time of poorest overall pump function on the 2nd and 3rd day coincides with an increased compliance of infarcted muscle reported at this time, while the later stiffening supports better overall ventricular performance (Hood *et al.*, 1970; Forrester *et al.*, 1972).

It is remarkable how much also the end-diastolic size of the left ventricle increased acutely, especially with the anterior infarctions. These data in man agree with those in experimental infarction which have indicated an immediate utilization of the Frank-Starling compensation mechanism in main-

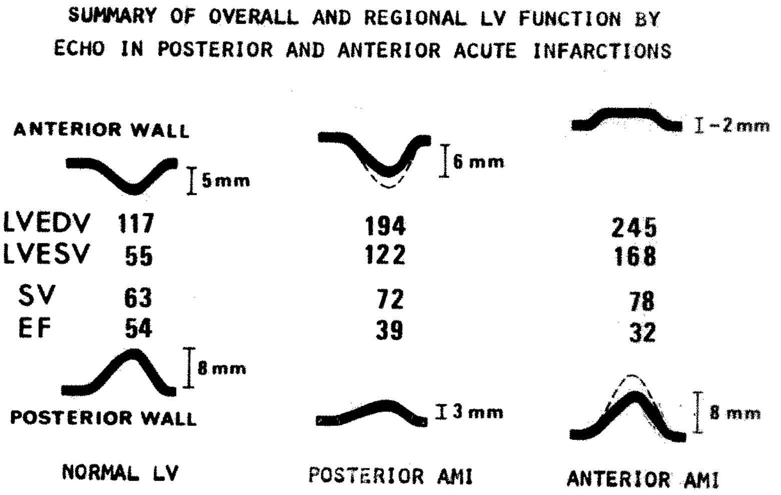

FIG. 7 *Average ventricular diameters and systolic motion of both the infarcted and the uninvolved segments are drawn for a normal ventricle and for posteroinferior and anterior acute myocardial infarctions (2nd day). Pump performance is poorest in the anterior infarctions, where the largest ventricular volumes with the lowest ejection fractions are seen, also with the greatest regional asynergic changes. Uninvolved segments show hyperfunction if considered in relation to chamber volume. The dotted lines represent overactive regional function often seen particularly in the uncomplicated infarctions.*

taining the normal stroke volume (Harley, Behar, and McIntosh, 1968; Heikkilä, Tabakin, and Hugenholtz, 1972). Among chronic heart diseases the highest preload stresses notably occur in subjects with coronary heart disease associated with segmental left ventricular asynergy (Ratshin *et al.*, 1974): such findings likewise reflect the grave nature of the postinfarction left ventricular dysfunction.

Echocardiographic studies of left ventricular end-diastolic or stroke volumes in acute infarction have so far been reported from a few small series of patients. Broder and Cohn (1972) stated that the left ventricular diameters remained normal in 5 patients despite high filling pressures of 28 to 36 mmHg (3·5 to 4·8 kPa), but Cahill *et al.* (1973) described in 17 patients increases of end-diastolic volume and decreases of ejection fraction which correlated with the clinical severity of acute infarction. In their study the end-diastolic volumes in the NYHA groups 3 and 4 were of the same magnitude (232 ml) as in the patients with anterior infarction in our series (246±25 ml). Stroke volumes by echocardiography have been of the same order as in our study (Pombo *et al.*, 1971; Ratshin, Rackley, and Russell, 1972; Smith *et al.*, 1974; Chapelle *et al.*, 1974).

The distinct acute changes in the left ventricular size in the present echocardiographic study agree excellently with the picture of acute myocardial infarction which was described in 38 patients evaluated within 48 hours from the onset of symptoms by Rigo *et al.* (1974) by biplane gated scintiphotography. The left ventricular end-diastolic volume was increased by +57 per cent in their heart failure group and by +118 per cent in the cardiogenic shock group, corresponding to the figures in the present series of +78 per cent, 208 ±92 ml, in the posterior, and +106 per cent, 246±25 ml, in the anterior infarctions. In their study the end-systolic volume was calculated from the biplane areas providing the best accuracy: the remarkable increases were +146 per cent and +320 per cent respectively, and the mean ejection fraction was 36 per cent. Here the increase in the anterior infarctions would result in figures of +230 per cent (168±58 ml), though the calculation of end-systolic volume from a single echo axis is in contrast to the end-diastolic volume, unsatisfactory because of systolic asynergy as discussed later. Another scintigraphic study also showed a similar high prevalence of abnormal volumes as was obtained here by echocardiography (Kostuk *et al.*, 1973).

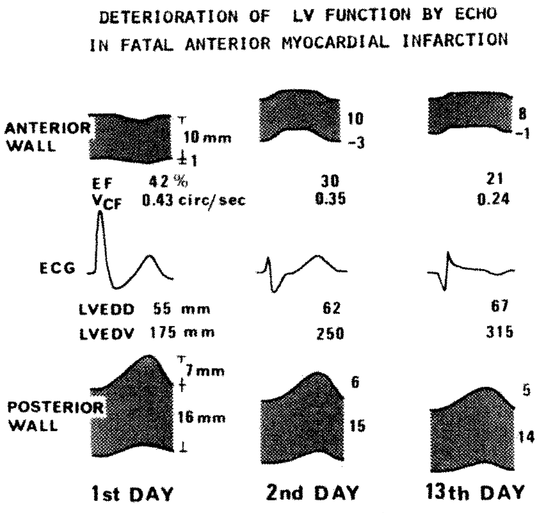

FIG. 8 *Echocardiographic monitoring of a progressive power failure. In this 34-year-old man the noninfarcted myocardium failed to compensate for an extensive and distinctly paradoxically moving anterior myocardial infarction. Ventricular volume became doubled and ejection fraction fell to one-third of the normal before death. Necropsy findings were displayed in Fig. 8 of our earlier report; Heikkilä and Nieminen (1975).*

Echocardiographic left ventricular function in anterior and posterior infarction

Greater depression of left ventricular pump function was evident by echocardiography in anterior myocardial infarctions than in posteroinferior ones. This finding concurs with the haemodynamic difference documented between anterior and posterior infarctions (Russell, Hunt, and Rackley, 1973). Regional function also was poorer in anterior infarctions: asynergy manifested as persistent paradoxical pulsation, as compared with less stable akinesia or hypokinesia in posterior ones, and the uninvolved myocardial regions tended to move less vigorously. These abnormalities may have been slightly modified by the superimposed recoil of the left ventricle as a whole. But the latter is a small and late systolic event (McDonald, Feigenbaum, and Chang, 1972), in contrast to what was seen in our patients when paradoxical motion was already maximal in the isovolumic phase, and similar to the findings noted in experimental infarction (Heikkilä *et al.*, 1972).

Serial changes in overall and regional left ventricular function

The serial monitoring of the left ventricular pump function was limited here to one week. Within this time the pump performance was poorest on the 2nd and 3rd days by all echo parameters. This course agrees with the results obtained with ultrasound (Wharton, Smithen, and Sowton, 1971), and with other methods (Thomas, Malmcrona, and Shillingford, 1965; Hood *et al.*, 1970; Heikkilä, Luomanmäki, and Pyörälä, 1971b; Rahimtoola *et al.*, 1972; Kostuk *et al.*, 1973; Gunnar *et al.*, 1974). Regionally, the serial deviations of the noninfarcted segments remained insignificant, remaining in the high normal range in the posterior infarctions, and falling to the low normal level in the anterior infarctions. However, here it should be recognized that even these normal values indicate enhanced segmental function in the presence of an enlarged left ventricle and high wall stress (Heikkilä *et al.*, 1972).

So far the function of the uninvolved myocardial segments has been estimated indirectly (Feild *et al.* 1972; Kitamura *et al.*, 1973; Rigo *et al.*, 1974). In echocardiography, regional changes in both the asynergic and the uninvolved segments may be monitored directly and serially. In clinical decision making, poor contractility of the uninvolved muscle segments detected in association with large acute infarction has, in our experience, been rewarding, as in these cases the clinical course has always been fatal despite aggressive treatment (Fig. 8).

Influence of asynergic contraction on echocardiographic measurements

Asynergically contracting segments have been of great concern when one has tried to evaluate ventricular function quantitatively by echocardiographic dimensional methods which are based on uniformity of the chamber shape (Paraskos *et al.*, 1971; Gibson, 1973; Ludbrook *et al.*, 1973; Popp *et al.*, 1973). These aspects naturally become relevant to the present study, where echocardiography demonstrated asynergic contraction in 100 per cent of the patients.

Theoretically, even large asynergic segments would not have much influence on volume calculations in *diastole* because nonuniform ventricular geometry appears only during systolic contraction. Derivation of the end-diastolic volumes by the echo diameter should thus be correct even in the acute phase of myocardial infarction because any local aneurysmal bulge which distorts diastolic shape of the ventricle takes weeks to develop. In chronic coronary heart disease, Sweet *et al.* (1973) similarly noted that asynergy mainly influenced the accuracy of calculating end-systolic and not end-diastolic left ventricular volumes.

Left ventricular end-systolic volume is more

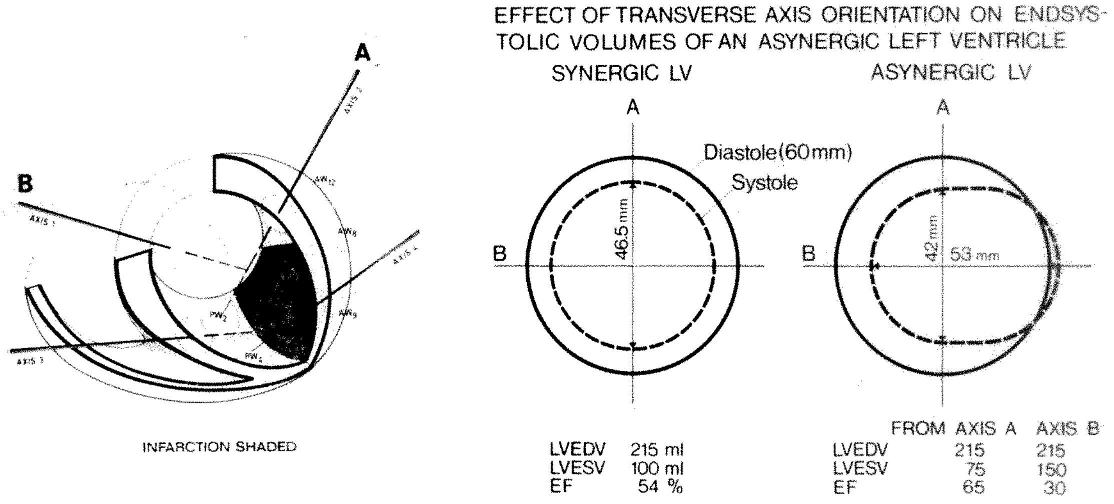

FIG. 9 *Diagrammatic cross-sections of left ventricle, to show distortion of volumetric analysis caused by asynergy. End-systolic volume varies depending on whether or not the transverse axis transverses asynergic (axis B) or noninfarcted regions (axis A). Since ventricular asynergy is systolic dynamic alteration, this is thought to have little effect on the symmetry of diastolic dimensions, at least in the early phases after myocardial infarction. The three-dimensional schema of the left ventricle shows the 4 major echobeam directions used in the echoventriculography method.*

subject to error because in asynergic systole one transverse axis measurement, or even a single plane angiographic silhouette (Vogel, Cornish, and McFadden, 1973), is no longer representative of the entire chamber. Whether the echo dimension traverses an asynergic segment or not, over- or underestimation of end-systolic volume results from the cube function (Fig. 9). In posterior infarction the methodological error will be in the direction of too large an end-systolic volume (axis B in Fig. 9). In contrast, in anterior infarctions (axis A in Fig. 9) the figure will most often be too low, particularly in large anterolateral infarctions not involving the septum. This was the case in 50 per cent of the anterior infarctions in this series. The shape distortion obviously applies also to the calculation of derived parameters of pump performance like ejection fraction and Vcf. However, when used serially, relative changes of these parameters may also be used in monitoring directional changes in the pump performance (Fig. 8).

The above differences are further related quantitatively, not only to the presence of, but also to the size and type of, motion of the asynergic segment. The size may vary greatly from 10 to 70 per cent of the left ventricular mass (Harnarayan *et al.*, 1970; Feild *et al.*, 1972; Kitamura *et al.*, 1973; Rigo *et al.*, 1974). Echocardiographically, the asynergic area is larger in anterior infarctions (Heikkilä and Nieminen, 1975), and also shows more paradoxical systolic outward motion, with corresponding influence on assessment of the actual end-systolic cavity size (Fig. 4 and 6).

When related to ventricular enlargement, one may calculate a theoretical sum of inward movement of the septum and posterior wall to represent a normal stroke volume of, for instance, 60 ml. For a normal-sized ventricle (LVEDD 50 mm) this figure is 10–11 mm; for a 200 ml end-diastolic volume (LVEDD 59 mm) seen here in posterior infarctions, 7 mm; and for 250 ml (LVEDD 63 mm) of the anterior infarctions, 5·5 mm. Deviation from such a 'normalized' sum of the amplitudes of wall motions (Fig. 7) suggests nonrepresentative muscle areas having been traversed by echobeam, functional mitral incompetence, or both.

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Duration of diastole versus cycle length as correlates of left ventricular ejection time[1]

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Studies were done on 82 normal subjects to evaluate cycle length versus duration of diastole as determinants of left ventricular ejection time. Cycle length and its reciprocal, heart rate, had the highest correlation with left ventricular ejection time. Removal of the self-correlation of left ventricular ejection time within cycle length reduces the correlation so that, of all intervals, duration of diastole had the highest correlation as a determinant of left ventricular ejection time. Cycle length and heart rate remain valuable as spuriously close but not misleading correlates for predicting or correcting left ventricular ejection time.

Time-based measurements of the cardiac cycle have proved to be useful correlates of cardiac performance. One well-studied measure of left ventricular function is the left ventricular ejection time (LVET). The relation of the ejection period to cardiac cycle length and stroke volume has been discussed in numerous studies of the determinants of LVET (Weissler, Peeler, and Roehll, 1961; Spodick and Kumar, 1968; Jones and Foster, 1964).

Stroke volume is directly related to LVET. Cycle length, usually expressed as heart rate, serves as a practical correlate of ejection time (Weissler *et al.*, 1961; Spodick and Kumar, 1968; Jones and Foster, 1964; Xenakis, Quarry, and Spodick, 1975; Spodick and St. Pierre, 1970) owing to its effect on stroke volume (Weissler *et al.*, 1961; Schlant, 1974; Harley, Starmer, and Greenfield, 1969). Differences in cycle length are caused mainly by differences in the duration of diastole, which, within limits, is a determinant of the duration of ventricular filling. Filling is a prime determinant of stroke volume and should be of central importance in determining ejection time. In theory, therefore, LVET should be more closely related to the duration of diastole than to the duration of the entire cycle. We examined the duration of diastole in comparison with cycle length as correlates of LVET.

Methods

Studies were made on 82 subjects (43 women and 39 men), ages 39 to 69. All had a normal history, physical examination, and 12-lead electrocardiogram. Supine resting recordings were made of simultaneous electrocardiogram and right carotid pulse curves. Intervals on the curves were measured independently of each other. Each value used in the analysis represents the mean of 5 measured cycles for each subject. Linear regression equations for left ventricular ejection time were calculated vs. cycle length, heart rate, diastolic interval, and cycle length *minus* LVET. Statistical differences in slopes were tested by the t test for slopes.

Terms

Cycle length (RR): RR interval of preceding cycle in milliseconds.
Heart rate (HR): 60,000/cycle length in beats/minute.
q: Initial deflection of QRS complex in lead II of the electrocardiogram.
CAR_u: Time from q to the onset of the rapid segment of the carotid upstroke (ms).
CAR_{In}: Time from q to the carotid incisura (ms).
Diastolic interval ($CAR_{In} \rightarrow q$): The time from the preceding carotid incisura to the q wave (ms). This diastolic interval closely approximates to the duration of diastole (Spodick, and St. Pierre, 1970; Craige, 1974; Tavel, 1972).

LVET was plotted against heart rate (HR), cycle

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TABLE 1 *Intervals and heart rates*

	LVET (ms)	*RR (ms)*	*HR*	*$CAR_{In}\rightarrow q$ (ms)*	*RR minus LVET (ms)*
Men	280±23·0	837±124 1	72·9±11·1	436±109·2	556±111·1
Women	295±30·4	833±161·8	74 0±14·9	411±134·4	539±138·9
Total	288±27·9	835±144 5	73·0±13·2	423±122·9	547±126·0

Values recorded are the mean ±1 standard deviation.

TABLE 2 *Data for regression $LVET=bX+a$*

X	*r*	*P (r)**	*a*	*b*	*P (difference in slope)**
HR	−0·69	0·001	395	−1·45	0·02
RR	0·70	0·001	174	+0 14	—
$CAR_{In}\rightarrow q$	0·63	0·001	227	+0·14	0·05
RR minus LVET	0·58	0 001	217	+0·13	0·05

*P values in second column are for significance of the correlation (r) of each factor (X) with LVET. P values in the last column are for differences in slope (b) for each factor and LVET compared with the RR-LVET slope.

length (RR), and diastolic interval ($CAR_{In}\rightarrow q$). Since RR includes the LVET, this was subtracted from RR to eliminate its autocorrelating influence, so that LVET was also plotted against RR *minus* LVET.

Results

The results are summarized in Tables 1 and 2.

The regression equations and correlation coefficients relating each variable to LVET were as follows:

Heart rate *vs.* LVET:
$LVET = -1{\cdot}45\ HR + 395$; $r = -0{\cdot}69$.
Cycle length *vs.* LVET:
$LVET = 0{\cdot}14\ RR + 174$; $r = +0{\cdot}70$.
Diastolic interval *vs.* LVET:
$LVET = 0{\cdot}14\ (CAR_{In}\rightarrow q) + 227$; $r = +0{\cdot}63$.
Cycle length *minus* LVET) *vs.* LVET:
$LVET = 0{\cdot}13$ (RR *minus* LVET)$+217$; $r = +0{\cdot}58$.

Discussion

The relation of LVET to heart rate and the level of correlation were similar to results in other series (Weissler *et al.*, 1961; Spodick and Kumar, 1968; Willems and Kesteloot, 1967). The level of correlation of LVET with cycle length (r=0·70) was essentially the same as for heart rate (r= −0·69). Since heart rate is derived from the fundamental measurement (cycle length), it is not surprising that the correlation was equivalent. It should be noted that the general relation of RR to LVET is curvilinear, but over the range of rates in this study it is virtually linear (Willems and Kesteloot, 1967).

LVET was expected to correlate best with the duration of diastole, which varies inversely with heart rate and is a major determinant of stroke volume. This was, however, not true. Diastole showed a lower correlation (r=0·63) with LVET than did cycle length. But the RR interval includes LVET and hence LVET is being partly correlated with itself. When LVET is plotted against cycle length excluding ejection time (ie, RR *minus* LVET) the level of correlation (r=0·58) is indeed lower. That is, LVET is less well correlated with cycle length when the autocorrelation factor is excluded.

These results unmask the autocorrelating factor and the resulting spuriously high correlation of LVET with cycle length (and heart rate), but they do not invalidate the use of RR or heart rate as indices for evaluating ejection time. The LVET vs. RR and LVET vs. ($CAR_{In}\rightarrow q$) regressions have parallel slopes, indicating equal proportionate influence of differences in each variable. Though the diastolic interval is most highly correlated with LVET, cycle length remains valuable as an easily measured practical correlate.

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Long-term results of arterial counterpulsation in acute severe cardiac failure complicating myocardial infarction

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Thirty patients were discharged from hospital after treatment with arterial counterpulsation for acute severe heart failure complicating myocardial infarction. Seventeen patients had been in cardiogenic shock—13 with power failure alone, and 4 with a mechanical complication which required corrective surgery. Thirteen patients were in impending or 'preshock'. The follow-up period after infarction averaged 13·1 months. Results were good in 'preshock' patients, and in shocked patients with a surgically correctable mechanical complication. Results were poor in shocked patients with power failure alone. Counterpulsation has an important supportive role in the treatment of complicated myocardial infarction, provided that intervention is prompt and mechanical complications, if present, are corrected early.

With ventricular fibrillation virtually eliminated as a cause of death in hospital after myocardial infarction, attention has focused on methods for treating cardiac failure which is now responsible for most hospital deaths and most late disability after infarction. The most promising new advance in this area is the counterpulsation system of ventricular assistance, which has been used effectively in treating cardiogenic shock, severe heart failure, and recurrent pain after infarction. Early results of such treatment have been reported from the Massachusetts General Hospital (Leinbach *et al.*, 1973; Sanders *et al.*, 1972) and other centres (Miller *et al.*, 1974; Mueller *et al.*, 1971; Scheidt *et al.*, 1973). Our own experience with arterial counterpulsation began in 1971 (O'Rourke and Chang, 1974; O'Rourke *et al.*, 1975). We report here long-term results of the first 30 patients who left hospital after treatment with arterial counterpulsation for acute severe heart failure complicating myocardial infarction.

Patients

In the 38-month period to 31 December 1974, 210 patients were referred for consideration of arterial counterpulsation. Of these, 62 with acute severe heart failure complicating myocardial infarction underwent counterpulsation. Thirty patients survived and were discharged from hospital. Follow-up was conducted in March 1975 and all patients were accounted for. All but 2 surviving patients were interviewed personally, and detailed information for these 2 (who lived outside Sydney) was obtained from the attending physician.

The patients had been divided into two groups—shock and 'preshock'. The definition of shock was a modification (O'Rourke *et al.*, 1975) of that proposed by the U.S. Myocardial Infarction Research Unit Program. 'Preshock' (O'Rourke and Chang, 1974) was a term applied to patients with acute severe refractory cardiac failure, accompanied by recurrent pain, recurrent ventricular arrhythmias or conduction disturbances, and who were deteriorating despite conventional medical therapy. Peel *et al.* (1962) and Norris *et al.* (1969) prognostic indices had predicted hospital mortality rates >90 per cent and >55 per cent, respectively, in the shock and 'preshock' groups. There were 17 hospital survivors in the shock group (of 46), and 13 hospital survivors in the 'preshock' group (of 16). The 17 survivors of cardiogenic shock were further divided into a subgroup of 13 with power failure alone causing shock, and a subgroup of 4 who survived correction of a mechanical complication which contributed to the shock state. These comprised one patient each with ventricular septal defect, haemopericardium with subacute heart rupture, haemopericardium from haemorrhagic infarct, and left ventricular aneurysm.

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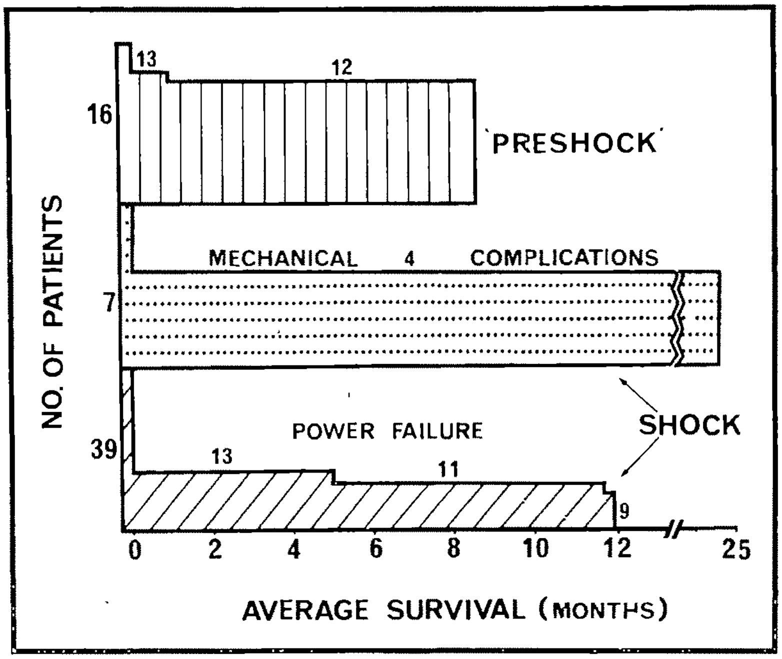

FIG. 1 *Survival rates in patients treated with arterial counterpulsation for acute myocardial infarction: there were 30 hospital survivors, comprising 13 of 16 with 'pre-shock', 4 of 7 with shock caused by mechanical complications, and 13 of 39 with shock caused by pure power failure.*

Results

Overall mortality rates are shown in Fig. 1. For shocked patients, results were best where mechanical complications were present. Of the 7 who underwent corrective surgery, 4 left hospital and there were no subsequent deaths on average follow-up of 24·5 months. Of the 39 shocked patients, without mechanical complications, there were 13 hospital survivors and 4 late deaths on average follow-up of 11·9 months. Sixteen patients were treated in hospital for 'preshock', with 13 hospital survivors, and one late death on average follow-up of 8·6 months. This patient died suddenly during uncomplicated convalescence, with evidence of acute recent coronary thrombosis at necropsy. The 4 patients who died after treatment for cardiogenic shock died in severe cardiac failure, without definite evidence of fresh reinfarction.

Quality of life after discharge from hospital was assessed according to functional activity. Each patient completed a detailed questionnaire (evolved in liaison with the National Heart Foundation N.S.W. Rehabilitation Unit), aimed at assessing symptoms, physical activity, and working ability. This was followed by personal interview of the patient, physical examination, chest x-ray examination, and resting electrocardiogram. Patients were classed as disabled, or as having returned to full-time or part-time (approximately 50% of the time) activities.

Again, 'preshock' patients gave encouraging results (Fig. 2). There was one death from fresh reinfarction. Two patients were disabled: one by low output failure, and one (though physically well) by cardiac neurosis. Six had returned to full-time previous activities and another 4 were expected to do so after further convalescence, giving an 83 per cent return to work for 'preshock' survivors. The 4 patients with shock and mechanical complications stand out. All 4 had returned to full-time previous activities and required minimal treatment. One of these patients held two jobs concurrently and was leading a more active life than previously. Results with shock from power failure alone were disappointing. Four patients had died after an average survival of 9 months (range 5 to 14 months), and these had all previously been disabled. Two survivors were disabled, both by low output failure, and these required maximal treatment. Five had returned to part-time activities, and only 2 to full-time work.

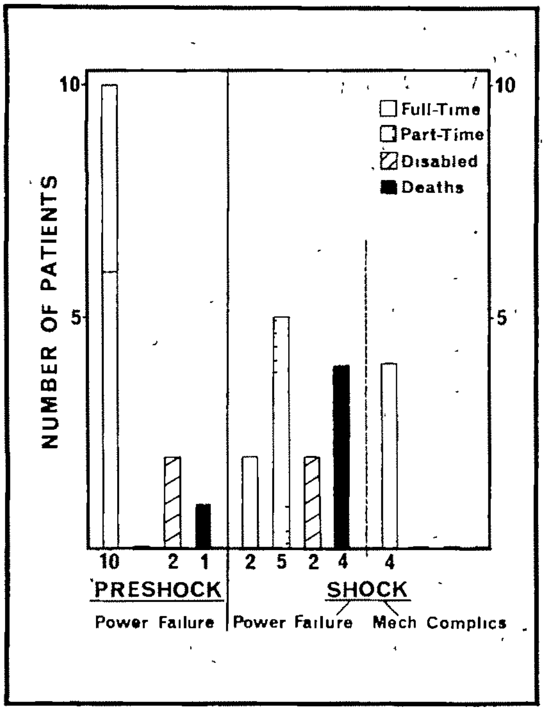

FIG. 2 *Functional status of the 30 hospital survivors.*

The experience with coronary artery bypass grafting in pure power failure after infarction is uncertain, 8 patients being treated with bypass grafting alone. Six patients were in cardiogenic shock, and 2 in 'preshock' with 3 hospital survivors and 1 death on follow-up. While revascularization surgery did not appear to benefit either in the short or long term, it is acknowledged that this is contrary to much of the current experience elsewhere (Miller *et al.*, 1974; Sanders *et al.*, 1972).

No long-term complications attributable to counterpulsation or surgery were found on follow-up. In particular there were no peripheral vascular complications attributable to the intra-aortic balloon.

Discussion

Of the 39 patients with cardiogenic shock as a result of power failure alone, only one-third left hospital and half of these were subsequently disabled by cardiac failure. Only 2 (5%) returned to full-time work. These results are disappointing though it would be unfair to suggest that counterpulsation is not warranted in this condition. Many of the patients in this group had been in shock for over 8 hours before counterpulsation was started and many were in established acute renal failure. It is now clear from experimental studies and from our results in impending or 'preshock' that to be most effective, counterpulsation must be initiated early. Our interpretation of results to date is that counterpulsation is warranted in patients with cardiogenic shock from pure power failure, provided that past health has been reasonably good and provided that shock has not been present for more than 8 hours. Our approach to aortocoronary bypass surgery in association with counterpulsation is currently under review. Revascularization surgery was performed on 6 of the 39 patients without results being demonstrably different from the group as a whole. More encouraging results have been reported from Boston (Miller *et al.*, 1974; Sanders *et al.*, 1972).

In contrast to the rather gloomy results in established cardiogenic shock resulting from power failure alone, results in patients with mechanical complications of infarction have been encouraging. It is clear that a high index of suspicion must be held for the mechanical complications of infarction—ruptured septum, ruptured papillary muscle, ruptured free wall with haemopericardium, or haemopericardium from haemorrhagic infarct—and that counterpulsation combined with appropriate corrective surgery provides every prospect for an excellent long-term result in such patients, again provided that intervention is prompt.

Results of counterpulsation in patients with massive infarction and impending or 'preshock' have been very good in both the short and long term. It is true that this condition cannot be defined with precision and that the progression to shock cannot be predicted with certainty. However, the patients as a group had a very poor prognosis for survival in hospital as gauged by Norris *et al.* (1969) and Peel *et al.* (1962) indices. Hospital death rate in this group (19%) was similar to the overall average for myocardial infarction treated in Australian coronary care wards (McLean, Penington, and Sloman, 1973). Long-term results were also good with only 1 of 13 patients being disabled by cardiac failure and with 10 of 13 patients returning to previous activities, and without any short or long-term complications of treatment.

We believe that the long-term results presented here justify early aggressive treatment of patients with severe heart failure complicating myocardial infarction. Good results are to be expected when intervention is early, and when mechanical complications, if present, are corrected early. Results are likely to be poor if mechanical assistance is delayed until after shock has been established for many hours.

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Design of exercise test, with special reference to heart patients

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Estimation of exercise tolerance in patients with heart disease and significant symptoms can usually not be expressed in terms of maximal oxygen uptake or power at a fixed heart rate calculated from a 'steady state' exercise test.

The exercise tolerance can be expressed only by the maximal power developed, when limited by symptoms. For this purpose the level of tolerance is better assessed by a test with small increments and short duration of each work load.

In clinical practice this type of almost continuous increase in load was found to be particularly useful in patients with ischaemic heart disease.

Comparative studies showed that the work per heart beat at equal loads is significantly higher in the test with continuous increase in load than in the test with steps of 6 minutes duration, both in normal subjects and in heart patients. The difference, however, is small (7%) and for practical purposes these tests have equal validity as a measure of the circulatory capacity.

Evaluation of the exercise tolerance from the history alone is often unreliable in patients with heart disease. Some patients with low capacity neglect symptoms. This is often observed in patients who are disabled since childhood and therefore have no experience of a normal circulatory function. Other patients exaggerate their symptoms or suffer from symptoms not associated with a low circulatory capacity. We therefore need methods for the objective determination of physical capacity. Exercise testing is also of great value as a tool to measure the effect of medical and surgical treatment. A simple procedure is to observe the patient climbing stairs. This is, however, not satisfactory as the work load is not well defined and objective recordings of circulatory variables cannot easily be obtained. Standardized exercise tests of different types have been used. The work must involve large muscle groups in order to give information of the oxygen transport capacity. Both treadmill and bicycle ergometer work fulfil this requirement. We prefer work on a bicycle ergometer as this can be accurately calibrated and thus the work intensity can easily be measured without determination of the oxygen consumption, and most patients, at least in Sweden, are familiar with pedalling a bicycle.

In healthy subjects the maximal aerobic power is determined by measuring the maximal oxygen uptake or the power developed when the maximal heart rate is obtained. Any further increase in work load will not result in a higher oxygen uptake or heart rate. Patients with severe heart disease are unable to perform such a maximal exercise test and, therefore, various types of submaximal exercise test have been devised. The report of a WHO meeting (World Health Organization, 1968) concerning exercise tests refers to four designs: type 1) single level load, type 2) discontinuous series of increasing loads with intermittent rest periods, type 3) nearly continuous increase in load, type 4) continuous series of increasing loads with an almost steady state at each level, each lasting at least 4 minutes (Fig. 1).

A patient with heart disease should not be suddenly exposed to a load close to his maximal tolerance and type 1, therefore, is not appropriate. Type 2 is tedious and at the highest level of work the state is suddenly changed from rest to a heavy load. Those most suitable for heart patients are types 3 and 4. To determine the aerobic power it is important to use a test that allows the patient to

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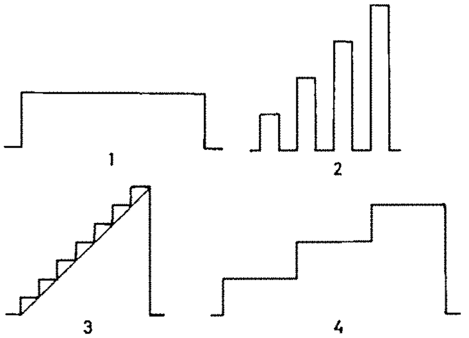

FIG. 1 *Schematic drawing of different designs of exercise tests. 1) Single level load. 2) Discontinuous series of increasing loads with intermittent rest periods. 3) Continuous or nearly continuous increase in load. 4) Continuous series of increasing loads with an almost steady state at each level.*

reach a steady state. This has been supposed to occur in the type 4. In Sweden this type of test has been widely used in clinical practice for nearly 30 years (Sjostrand, 1947; Wahlund, 1948). The work lasts for 6 minutes at each load, and with 3 or 4 equal increments the subject should reach a heart rate of about 170 beats per minute. Using the linear relation between load and heart rate, the work at heart rate 170/min is calculated and the exercise performance is expressed as the power (in Watts or kpm/min) at rate 170. In older patients the maximal heart rate is lower than this and a reference rate of 130 or 150 has been used (Strandell, 1964). Sometimes the work is stopped before completion of the 6-minute exercise period. The exercise tolerance then is not indicated by the highest power only but also by the working time. A patient who is able to work for 6 minutes at a certain load plainly has a better tolerance than the one who stops the same work after 2 minutes, though the same power output is achieved. In this case Strandell predicted the 'maximal' power by adding a figure proportional to the completed part of the period at the next higher load (Strandell, 1964).

For some years the type 3 work test, with small increments and each step lasting one minute, has also been used in our department. The purpose of this report is to compare tests of type 3 and type 4, in order to define the relative merits of each.

Subjects and methods

The usefulness of the exercise test with increasing loads, each step lasting for 6 minutes (type 4), was studied in heart patients referred to the laboratory for preoperative evaluation. From the records a consecutive series of 100 patients was selected. These patients with valvular lesions, congenital heart defects, or coronary heart disease had a wide range of exercise capacities.

A comparison between exercise tests of type 3 and type 4 was made in two groups of healthy subjects. The first group included 7 men and 7 women from the hospital staff, aged between 25 and 57 years, The second group consisted of 24 men, aged 18 to 20 years, entering military service. This comparison was also made in 28 patients with ischaemic heart disease and 23 patients with various acquired and congenital heart diseases. All these patients were referred to the department for preoperative evaluation and were suffering from significant symptoms.

The effect of total duration of work using the type 3 test was also studied in the 14 healthy members of the hospital staff, by performing two tests, one with increments of load twice the other, resulting in half the working time.

All tests were performed in the sitting position on an electrically braked bicycle ergometer (Elema). A 12-lead electrocardiogram was recorded before and after the test, and during the work period 6 chest leads were recorded continuously. Heart rate was counted from the electrocardiogram at the end of each period. In the healthy subjects the work load was increased to exhaustion, but it was not determined whether levelling off of oxygen uptake or heart rate had occurred. In the patients with heart disease the work load was increased until significant symptoms occurred. Most patients stopped the work when they were *unable* to continue, but in ischaemic heart disease the patients were asked to stop when the chest pain was of the degree they were accustomed to tolerate during their daily activity. In patients with aortic stenosis the test was ended at the appearance of symptoms and not continued to maximal tolerance if the patient suffered from angina, dyspnoea, or dizziness.

When the two types of test were compared in the same patient, exercise was stopped at about the same severity of symptoms. A doctor with wide experience of exercise tests was present during the procedure and evaluated the symptoms and the signs of strain. In all studies where each individual performed two tests, these were done on two consecutive days at the same time of the day and on the same ergometer. The order of the tests was ramdomized.

'Maximal power' (Strandell, 1964) was calculated by adding to the maximum work load at which the subject completed 6 minutes of exercise a proportion of the next increment of load corresponding to the proportion of the 6-minute exercise period completed.[1]

Student's paired t-test was used to test the significance of differences between mean values.

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[1] For example, if a patient completes a 6-minute exercise period at 60 Watts and then stops after 3 minutes at 90 Watts, the 'maximal power' is $60+\left(\frac{3}{6}\times 30\right) = 75$ Watts.

Results

Continuous exercise with increasing loads and steps of 6 minutes duration (type 4)

The original design of the test required that a steady state should be obtained, and at the highest load the heart rate should be close to 170 per minute. These two criteria were tested in 100 heart patients. From Fig. 2 it is evident that very few patients reached a steady state of the heart rate.

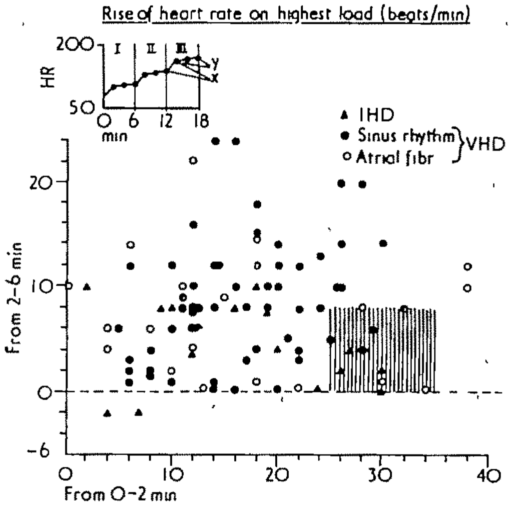

FIG. 2 *Exercise test with steps of 6 minutes duration in 100 patients with heart disease. Increase in heart rate from 2 to 6 minutes of work on the highest load (y-axis) in relation to the increase of heart rate during the first 2 minutes of work on the highest load (x-axis). The schematic diagram in the upper left part of the figure represents an ideal heart rate response, with a 'steady state' at each work level, and heart rate reaching 170/min after three increments of work load. Patients with this type of response will be located within the shaded area of the main diagram. Very few patients are in a 'steady state'.*

An ideal test should follow a pattern indicated in the upper right part of the diagram. Assessment of a steady state has been defined as an increase in heart rate of less than 10 beats a minute between the second and sixth minutes (Sjöstrand, 1967). Using these criteria the symbols in the diagram should be located within the shaded area: very few are. From Fig. 3 it is also evident that many patients do not reach a heart rate close to 170 per minute. The patients stopped exercising at lower heart rates because of symptoms, such as respiratory distress, chest pain, general fatigue, or tiredness in the legs. Often the work was stopped before the end of a 6-minute period. An evaluation of the exercise tolerance according to the original design of the test was, therefore, possible only in a few patients.

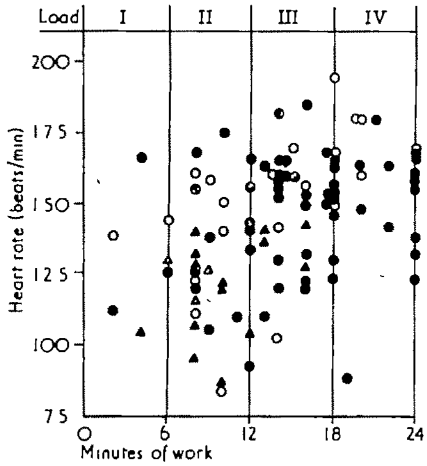

FIG. 3 *Exercise test with steps of 6 minutes duration in 100 patients with heart disease. Duration of work (x-axis) in relation to heart rate (y-axis) at the end of work. Some patients stopped exercising on load I and a few could continue to load IV. Many patients ended the work at a heart rate below 150/min.*
▲ *Ischaemic heart disease.*
● *Sinus rhythm,* ○ *atrial fibrillation, in patients with other forms of heart disease.*

Comparison between tests with steps of 6 minutes duration (type 4) and 1 minute duration (type 3) in healthy subjects

Performance in the two tests was expressed as the work-pulse (i.e. work per heart beat) and calculated as:

$$\frac{\text{Watts} \times 60}{\text{beats/minute}} \text{ (Joules/beat)}$$

This was calculated from the highest load that was completed in *both* tests to make comparison between the two tests possible, since many subjects were able to work on a higher load in a type 3 test. In the healthy subjects from the hospital staff there was on average a 7 per cent higher work-pulse in the type 3 than in the type 4 test (Fig. 4). The difference was highly significant ($P < 0{\cdot}001$). The subjects represented a wide range of physical fitness, with a variation of work-pulse from 36·0 to 102·1 J/beat. The mean duration of work at type 4 test was 22 minutes and at type 3 test 14 minutes. The work-pulse in the young men on military service varied between 46·2 and 81·6 Joules (Fig. 5). The average work-pulse for the type 3 test was 64·8 and for the type 4 test

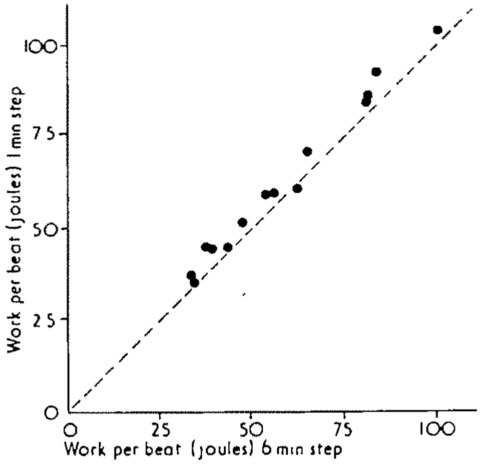

FIG. 4 *Relation between tests with steps of 6 minutes duration (x-axis) and 1 minute duration (y-axis) in 14 healthy subjects aged 25 to 57 years. The exercise performance is expressed in work per heart beat.*

60·0 J/beat. This difference of 8 per cent was highly significant (P < 0·001). The mean duration of the two tests was 15 and 16 minutes, respectively; this difference is not significant.

Effect of duration of work on heart rate

The increase of the load for each step must vary according to the subject's work capacity. If equal steps were used for all subjects the total working time would be very short for some and in others very long. It is, however, complicated to standardize a test where all individuals will reach the highest load within a predicted time (Arstila, 1972). The effect of variation in total working time by difference in increments of load is shown in Fig. 6. No difference of work-pulse was observed. The total work performed at low increments was 88·0 kJ and at high increments 51·2 kJ. Within this variation of working time, 14 and 7 minutes, respectively, the heart rate is dependent only on the power developed and not on working time or total work performed.

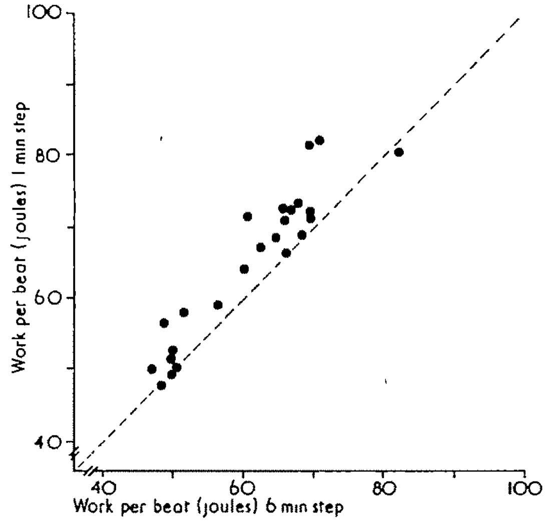

FIG. 5 *The same relation as in Fig. 4 in 24 healthy men aged 18 to 20 years.*

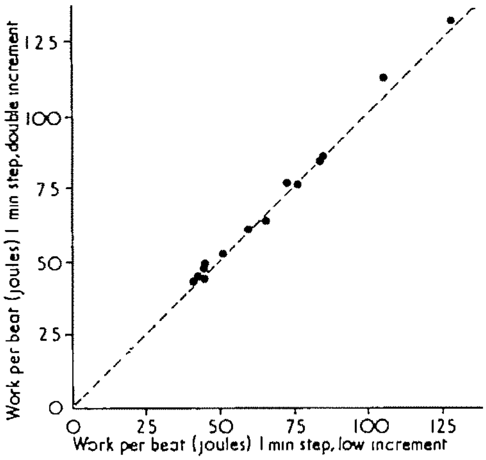

FIG. 6 *Relation between two work tests with steps of 1 minute duration in 14 healthy subjects. The y-axis represents tests with increments of each step twice that of the x-axis. The total duration of work during tests on the y-axis are half of the tests on the x-axis.*

Comparison between tests with steps of 6 minutes duration (type 4) and 1 minute duration (type 3) in patients with heart disease

A. Ischaemic heart disease Chest pain was the limiting symptom for exercise performance in all patients. When comparing the work-pulse, the highest load that was completed at both tests was used for the calculation; no difference was found (Fig. 7). The maximal heart rate obtained when the test was ended because of pain was on average 5 per cent higher in type 3 tests than in type 4 (P < 0 05) (Fig. 8). The highest load the patient could achieve was 19 per cent higher with the type 3 test than with type 4 (P < 0·001) (Fig. 9). In type 4 tests some patients had to discontinue exercise before completion of a 6-minute period, in some cases after only 1 minute. In type 3 tests the 1-minute period was always completed.

If a correction is made for incomplete exercise

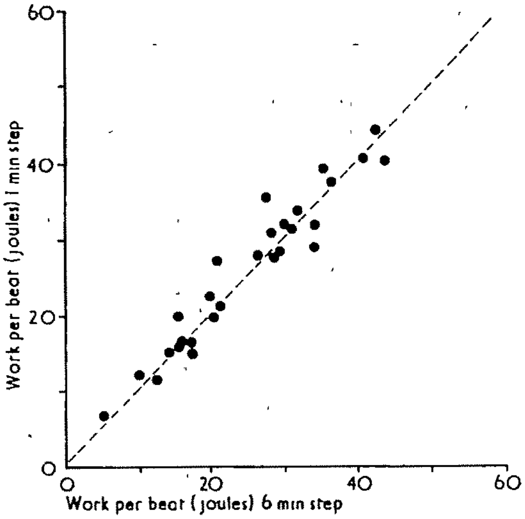

FIG. 7 *The same relation as in Fig. 4 in 28 patients with ischaemic heart disease.*

periods as suggested by Strandell (1964) in the type 4 tests, the difference between the two tests was greater, type 3 then being 41 per cent higher than type 4 (P < 0·001). The average duration of work was 10·0 minutes for the type 3 tests and 12·6 minutes for type 4. The average total work performed was 32·2 kJ for the type 3 tests and 38·4 kJ for type 4.

B. Valvular and congenital heart disease The work-pulse, calculated as for patients with ischaemic heart disease, was on average 7 per cent higher for type 3 tests. This difference was significant (P < 0·01) and more obvious for patients with a work pulse over 60 Joules than for patients with lower values (Fig. 10). The maximal heart rate obtained was on an average 2 per cent higher in type 3 tests than in type 4 tests (P > 0·3) (Fig. 11). The highest load achieved was 14 per cent higher during the type 3 test (P < 0·01) (Fig. 12). When Strandell's correction was made, the difference was 29 per cent (P < 0·001). The average duration of the work was

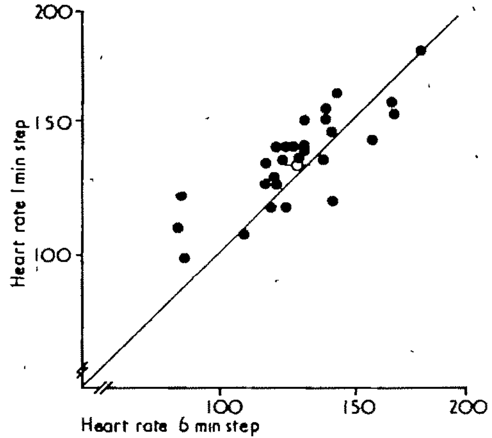

FIG. 8 *Relation between highest heart rate obtained during tests with steps of 6 minutes duration (x-axis) and 1 minute duration (y-axis) in 28 patients with ischaemic heart disease. The open circle represents the mean of the group.*

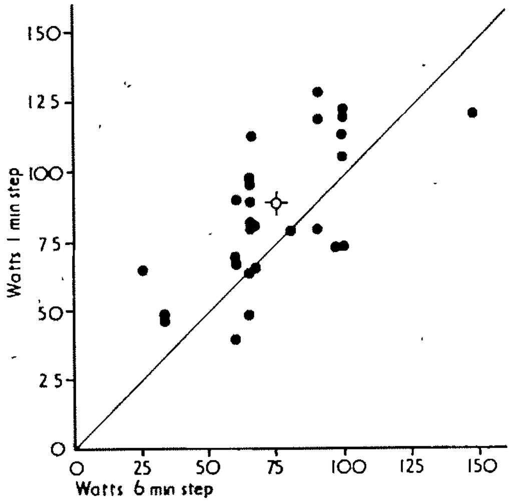

FIG. 9 *Relation between highest load achieved during tests with steps of 6 minutes duration (x-axis) and 1 minute duration (y-axis) in 28 patients with ischaemic heart disease. The open circle represents the mean of the group.*

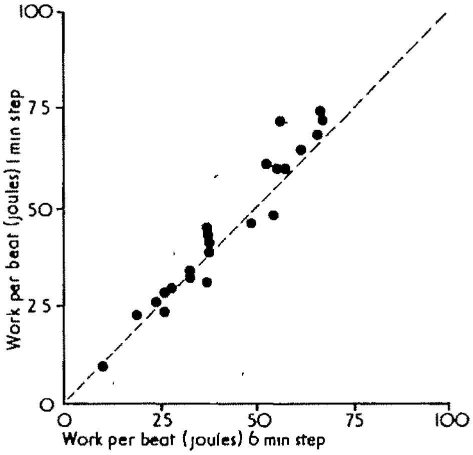

FIG. 10 *The same relation as in Fig. 4 in 23 patients with valvular or congenital heart disease.*

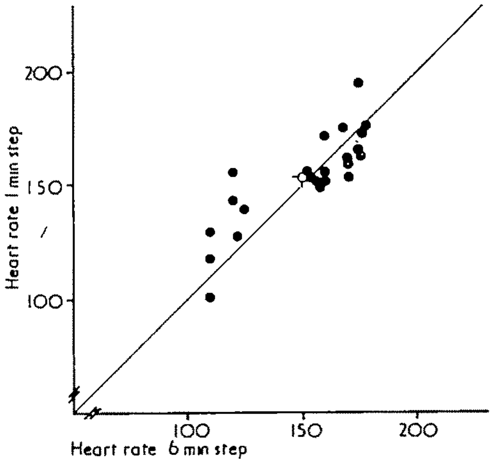

FIG. 11 *Relation between highest heart rate obtained during tests with steps of 6 minutes duration (x-axis) and 1 minute duration (y-axis) in 23 patients with valvular or congenital heart disease. The open circle represents the mean of the group.*

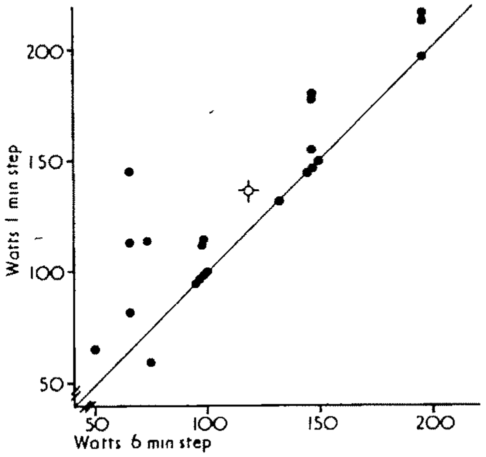

FIG. 12 *Relation between highest load achieved during tests with steps of 6 minutes duration (x-axis) and 1 minute duration (y-axis) in 23 patients with valvular or congenital heart disease. The open circle represents the mean of the group.*

7·8 minutes for the type 3 test and 14·3 minutes for the type 4 test.

Discussion

An exercise test must be adapted to the subjects who are examined and to the purpose of the test. For estimation of the maximal aerobic power the maximal oxygen uptake or the power developed (steady state) at the maximal heart rate must be measured. This test cannot be used in patients with severe heart disease. The term 'maximal working capacity' is, however, sometimes used also in clinical tests without any objective definition. Often it is used for the work load before the patient has to discontinue exercise on account of various symptoms, even when this occurs at rather low heart rates. This does not indicate the maximal circulatory capacity and the term 'maximal working capacity' should not be used.

The power at a given submaximal heart rate, e.g. 170 beats per minute, is a measure of the circulatory capacity (Sjöstrand, 1967). During work the oxygen uptake increases in a linear relation to the increase of work load and (at high heart rates) the mechanical efficiency is almost constant in different subjects (Åstrand, 1952). The oxygen uptake at heart rate (HR) 170 is a function of the stroke volume (SV) and the arteriovenous oxygen difference (AVD) according to Fick's equation ($\dot{V}o_2 = HR \times SV \times AVD$). Consequently the power or work-pulse at a heart rate of 170 is also a function of stroke volume and arteriovenous oxygen difference. In healthy individuals a linear relation exists between the power at a heart rate of 170 and such circulatory measurements as heart volume, blood volume (Kjellberg, Rudhe, and Sjöstrand, 1949), stroke volume (Bevegård, Holmgren, and Jonsson, 1963), and maximal oxygen uptake (Åstrand, 1952).

This type of test, however, cannot be used in patients with heart disease and severe symptoms. Because of lack of a steady state and a low heart rate on the highest load, an extrapolation to heart rate 170 has no validity (see Fig. 2). The exercise tolerance can only be expressed by the maximal power obtained when work is ended because of symptoms. The type and degree of limiting symptoms should be described, and the highest heart rate obtained should be indicated. The level of tolerance is best defined by a test with small increments and short duration of each step, to avoid a very long duration of the test. A design with steps lasting 1 minute is appropriate. In patients with low tolerance the total working time then will be 5 to 10 minutes with increments of 10 Watts. If this type of test is compared with the so-called steady state test with 6-minute steps, a very small difference is found in work-pulse both in healthy subjects and a group of patients with heart disease with a wide range of exercise tolerance. Therefore, both tests are equally valid as a measure of the circulatory function expressed as the power at heart rate 170.

Most patients with ischaemic heart disease in this study had a low exercise tolerance. The difference in duration of work in the two types of test was small. The patients continued the work to a slightly higher heart rate (5%) and a higher load (19%) during the test with steps of 1 minute than during the test with steps of 6 minutes duration. This greater difference for maximal load than for maximal heart rate in spite of equal work-pulse seems contradictory. The work-pulse, however, was calculated from *equal* loads completed for 6 minutes and 1 minute, respectively, during the two tests. When an additional load is performed during the test with 1-minute steps the heart rate does not rise proportionally to the increase in work-pulse, with increasing load.

Although the maximal power for the test with 6-minute steps was smaller than for 1-minute steps, the total work performed was significantly greater. This may explain the lower maximal load obtained. Measuring total work as an index of exercise tolerance of rather short duration is, however, useless both in normal subjects and, even more, in patients with heart disease. Measurements of power or work per heart beat give a better indication of myocardial stress than working time *per se*. Thus, a wide range of total work can be achieved in the same patient, depending on the magnitude of load and the duration of the test.

In patients with angina pectoris, the exercise tolerance is defined as the power developed when chest pain occurs, which is equal in character and severity to what the patient is used to in his daily life. This level is best measured by a test with a continuous or almost continuous increase of the load. Then the tolerance can be expressed as power developed without correction for working time. The duration of the test should be more than 3 minutes (Redwood *et al.*, 1971) and should not exceed 15 to 20 minutes. A continuous increment of 10 Watts every minute will satisfy this in most patients, as very few will perform more than 150 to 200 Watts. When the effect of treatment is studied the same design should be used for the test before and after treatment of each patient. The reproducibility of a single exercise test with 1-minute steps, calculated from duplicate determinations performed within 4 days in a group of patients with similar severity of coronary artery disease was found to be 6·6 per cent (Åström and Vallin, 1974).

A further advantage of the continuous type of test is the low starting load where the first loads can be looked upon as a warming-up period. The critical choice of the correct increments of load is also avoided, when too large increments might be dangerous for the patient.

Though both types of test seem to give about the same information, the type 3 test with 1-minute steps is more suitable for patients with low physical capacity, and furthermore is less time consuming. It can be completed in less than half the time required for the test with 6-minute steps.

Conclusions

In patients with heart disease and significant symptoms an estimation of exercise tolerance can usually not be expressed in terms of power at heart rate 170 beats per minute using a test with increasing loads each lasting for 6 minutes. Most patients stop working at much lower heart rates because of various symptoms, and a steady state is not obtained. The exercise tolerance is better defined by a test with continuous or nearly continuous increase in load.

In normal subjects the work performed per heart beat (work-pulse) at equal loads is significantly higher in the test with nearly continuous increase in load than in the test with steps of 6 minutes duration. The difference, however, is small and for practical purposes both tests have equal validity, even as a measure of the circulatory capacity expressed as the power at heart rate 170, both in healthy subjects and patients with heart disease.

If the working time is less than 15 minutes, a variation of the duration to half that time does not influence the work-pulse. Furthermore, the heart rate is determined by power and not by total work or duration of the test.

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Case reports

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Biloculate false aneurysm of the right ventricle after cardiac surgery

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A case of a 12-year-old boy who had double false aneurysms of the right ventricle after incomplete closed pulmonary valvotomy six years earlier is presented. The aneurysms were successfully treated surgically, and the aetiology is discussed.

False ventricular aneurysms are a rare and potentially fatal complication of cardiac surgery. They are less common than true aneurysms (Hurst, Fine, and Keyes, 1963; Littler, Meade, and Hamilton, 1971; Rosenthal, Gross, and Pasternac, 1972; Van Tassel and Edwards, 1972) but are more likely to rupture (Hunter and Benson, 1933; Gobel, Visudh-Arom, and Edwards, 1971; Van Tassel and Edwards, 1972; Rosenthal *et al.*, 1972). Both types of aneurysms are more frequent sequelae of operations on the left ventricle (Littler *et al.*, 1971).

This report describes what we believe to be a unique case of a patient who, after a closed pulmonary valvotomy, developed a false right ventricular aneurysm. This aneurysm, in turn, had ruptured into the left pleural cavity, resulting in a second false chamber. The patient survived this event and surgical correction of the lesion followed successfully.

Case history

A 12-year-old West Indian negro boy was born normally at full term. His mother had had rubella in the first month of pregnancy, and a heart murmur was discovered when he was 3 months old. He failed to thrive and was prone to upper respiratory tract infection. In 1967, at the age of 5 years, the diagnosis of pulmonary stenosis was made, and a transventricular pulmonary valvotomy was performed through a left thoracotomy. Apart from transient early postoperative pulmonary collapse and infection he maintained a gradual progressive improvement. Three years later he experienced slightly reduced exercise tolerance. In May 1973 a routine chest radiograph disclosed a widened mediastinum and a large round opacity in the upper left lung field. A right ventricular aneurysm was suspected. Two months later he was referred to the Hammersmith Hospital. His only symptom was a slightly reduced exercise tolerance.

On examination he was a thin, fit young boy. His arterial pressure was 110/80 mmHg (14.6/10.6 kPa), his pulse rate 100 per minute and regular; the jugular venous pulse was 2 cm above the sternoclavicular joint, with a prominent 'a' wave. There were distinct visible pulsations at the second and third left intercostal spaces. A grade 4/6 ejection systolic murmur was heard at the pulmonary area, with grade 3/4 pulmonary diastolic murmur. There were no signs of heart failure, and the previous thoracotomy was well healed, with a keloid scar. Routine laboratory investigations were normal. The chest radiograph showed a large right ventricle and slightly oligaemic lung fields. A large rounded shadow was superimposed on the main pulmonary artery and extended, just above it, into the upper left lung field. The lateral view showed anteroposterior extension of the mass (Fig. 1).

The *electrocardiogram* showed right axis deviation and right ventricular hypertrophy.

Cardiac catheterization disclosed a residual gradient of 60 mmHg (8.0 kPa) across the pulmonary valve: MPA pressure 30/13 mmHg (4.0/1.7 kPa), RV body 90/21 mmHg (120/2.8 kPa), pressure within aneurysm 89/15 mmHg (11.8/2.0 kPa).

The *cineangiocardiogram* of the right ventricle showed a centrally placed mediastinal aneurysm above and anterior to the heart, which filled by a jet from the right ventricular infundibulum. This mediastinal sac, in turn, communicated with and filled a posterolaterally placed sac in the left pleura.

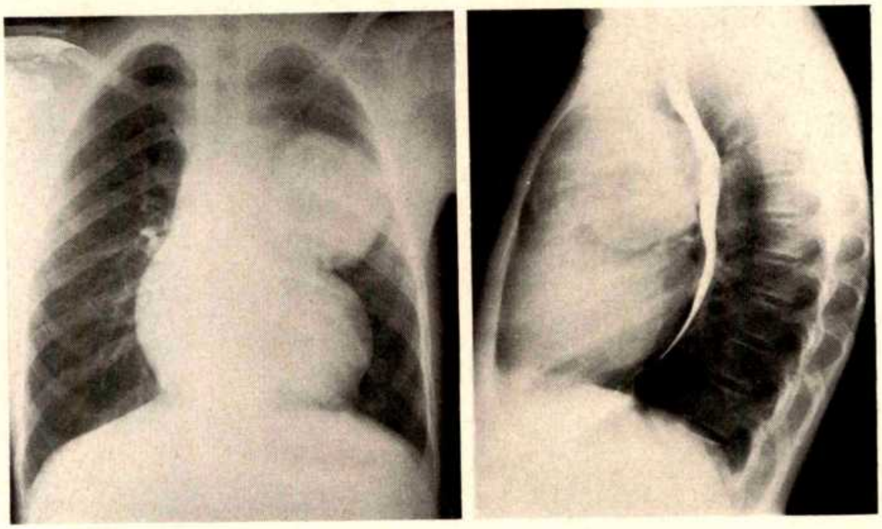

FIG. 1 *Preoperative posteroanterior and lateral chest radiographs showing a large right ventricle, and a large rounded central shadow superimposed on the pulmonary trunk and extending to the upper left lung field. The mass extends antero-posteriorly on the lateral view.*

The main pulmonary artery was displaced backwards and was compressed by the mediastinal aneurysm. No communication could be demonstrated between the pulmonary trunk with its two branches and either of the two aneurysmal sacs. Injection of contrast medium into the superior vena cava disclosed the close proximity of the juxta-atrial part of the superior vena cava and of the right atrial appendage to the mediastinal aneurysm. The appearance was that of a fairly large right ventricular aneurysm communicating with a second aneurysmal chamber in the left pleura.

Operation (H.H.B.)

In view of the angiographic findings and the intimate relations of the superior vena cava and the right atrial appendage to the central aneurysm sac, the risks involved in using a median sternotomy approach were appreciable. The right femoral artery, therefore, was cannulated, and a right anterolateral thoracotomy was performed through the fourth intercostal space. This approach provided trouble-free access to cannulate both cavae. Total cardiopulmonary bypass was established, the mediastinal aneurysm was freed from the back of the sternum, and the sternum was then divided transversely. The aneurysm was a false sac formed by the pericardium. It was opened anteriorly and found to communicate with the right ventricular infundibulum through a 1.5 cm elliptical hole, presumably the site of the previous ventriculotomy. Another 1.5 cm hole, laterally placed in the wall of the central aneurysm, led to the second false aneurysm formed by the adherent left pleura (Fig. 2). Neither cavity contained any thrombus.

The pulmonary trunk was incised longitudinally through the posterior wall of the mediastinal aneurysm to relieve the residual obstruction. The pulmonary valve was thickened, the commissures were fused, and the cusps were rolled in. It was evident that the pul-

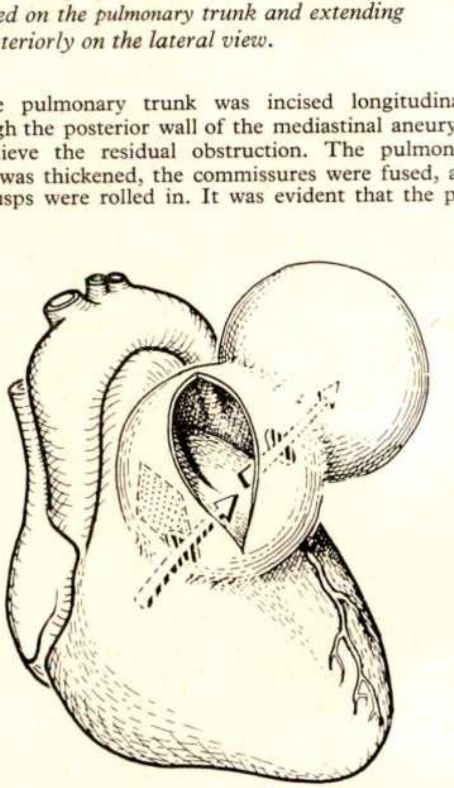

FIG. 2 *A diagram demonstrating the sites and communications of the two aneurysmal chambers and the inserted Dacron patch to relieve the residual obstruction (diamond-shaped dotted area).*

monary valve was regurgitant, with severe residual stenosis.

The arteriotomy was then extended across the pulmonary ring down to the ventriculotomy dehiscence. Part of the pulmonary valve cusps were excised as well as some infundibular muscle. A diamond-shaped woven Dacron gusset was inserted to enlarge the outflow tract, pulmonary valve ring, and artery and to close the ventricular dehiscence. The central aneurysmal sac was partially excised and drained. The lateral aneurysmal sac was drained via its communication with the central sac, and the two drains were connected to an underwater-seal-suction system. The patient came off bypass uneventfully and the chest was closed routinely. The immediate postoperative chest radiograph showed residual left pleural thickening but otherwise was satisfactory. The child had a smooth postoperative course and was discharged home on 28 August 1974.

Discussion

The majority of the recorded false aneurysms of the heart are related to myocardial infarction or surgery on the ventricles (Hurst *et al.*, 1963; Littler *et al.*, 1971; Fadali *et al.*, 1974). False aneurysms of the right ventricle are less common and follow surgery or trauma. Usually a false aneurysm follows a leak from the right ventricular outflow patch in the surgical correction of Fallot's tetralogy (Payne and Kirklin, 1961; Bahnson *et al.*, 1962; Wada *et al.*, 1965), but, whether the ventriculotomy itself or the patch dehisces, the main aetiological factor is the persistence of residual outflow obstruction producing raised right ventricular pressure. This was certainly a factor in our case.

If the patient is to survive the right ventricular dehiscence, there must be coexisting pericardial adhesions to prevent fatal tamponade (Hurst *et al.*, 1963; Stansel, Julian, and Dye, 1963; Fadali *et al.*, 1974). A unique feature of this case is the further rupture of this fasle aneurysm into the left pleural space, which must have been limited by adhesions, a result of the previous thoractomy – hence the development of the second false chamber. There is no way of knowing whether this second rupture occurred simultaneously with the ventricular dehiscence.

This patient had a regurgitant pulmonary valve and a chest infection after the initial valvotomy. Both these conditions have been suggested by Hipona and Bloom (1965) as being possible factors in aneurysm formation. Other factors, in childhood, such as residual left-to-right shunts and complete heart block (Payne and Kirklin, 1961), congenital defects of the myocardium, traumatic myocardial necrosis, and Chagas's disease have also been blamed (Bahnson *et al.*, 1962). On the whole aneurysms of the right ventricular outflow tract probably have a variety of causes.

Hurst *et al.* (1963) have suggested that the diagnosis of true versus false aneurysm cannot often be made preoperatively. However, our findings agree with Rosenthal *et al.* (1972) that false aneurysms tend to expand posteriorly and to the left upwards, and can reach a large size; and angiography in our case was strongly suggestive of false aneurysm.

Mirowski, Mehrizi, and Shah (1964) wondered whether the formation of keloid is in any way related to the development of ventricular aneurysm. They described a cardiac aneurysm at the site of right ventriculotomy in a patient with increased tendency to form keloid. It is interesting that our patient had developed keloid in his thoracotomy scar.

We agree with other authors in advising early surgery for false aneurysms. Indeed our patient was fortunate to come to surgery after surviving the development of double false aneurysmal sacs. The specifically designed surgical treatment helped to bring about the successful result (Jacobs, de Leval, and Stark, 1974).

Acknowledgment is made to Professor H. H. Bentall, Professor of Cardiac Surgery, The Royal Postgraduate Medical School, for permission to publish this report.

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Retrograde His bundle deflection in bundle-branch re-entry

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Atrial echo beats resulting from a reciprocating mechanism involving the bundle-branches were produced by premature atrial impulses in a patient with an A-V nodal bypass tract. The mechanism of the arrhythmia was suggested by the presence of a retrograde His bundle deflection which appeared 'sandwiched' in between a QRS complex with complete right bundle-branch morphology and a negative P wave. Though at a shorter cycle length the His bundle was still activated retrogradely echo beats were not seen because the retrograde H deflection occurred too early, when both bypass tract and A-V node were still effectively refractory. At the faster driven rate concealed retrograde activation of the right branch (by the premature impulse) was responsible for the right bundle-branch block patterns shown by the post-premature driven beat.

In a recent communication Varghese *et al.* (1974) discussed several tracings showing atrial echo beats which could have resulted from a reciprocating mechanism involving the bundle-branches. However, they could not make the differential diagnosis between intra-His bundle re-entry and bundle-branch re-entry because retrograde His bundle deflections were not seen. The present report deals with a case in which the recording of both antegrade and retrograde His bundle electrograms proved that some atrial echoes indeed result from bundle-branch re-entry.

Case report

A 31-year-old man with a short P-R interval and a history of repetitive supraventricular tachyarrhythmias was referred to the cardiovascular laboratory for electrophysiological evaluation. His bundle studies were performed as previously described in our laboratory after explaining the procedure and obtaining consent (Castillo and Castellanos, 1970, 1971). Fig. 1 was recorded during stimulation of the right atrium in the vicinity of the inferior vena cava. Driving cycle length was 670 ms. The duration of the corresponding intervals of the first (driven) beat was as follows: A1–H1 45 ms; H1–V1 45 ms. The QRS complexes measured 85 ms. The short atrio-His conduction time was attributed to the presence of a total or almost total A-V nodal bypass tract.

Atrial echo beats involving the bundle-branches were produced by a premature impulse (A2) delivered at a coupling interval of 330 ms. Because of the existence of an A-V nodal bypass tract A2 traversed the His bundle early enough to find the right bundle-branch completely blocked (Fig. 1). However it was conducted to the left ventricle with considerable delay through the left bundle system, thereafter crossing the septum in a left to right direction to activate the right bundle-branch in a retrograde fashion and re-excite the His bundle also retrogradely. Finally, the impulse reached the atria through the A-V node. The corresponding P wave was negative in leads II and III and had a low right atrial-high right atrial activation sequence which was different than that of driven (A2) impulses (Fig. 1). The duration and significance of the pertinent intervals is shown in the Table. To our knowledge, this is the first report in which a retrograde His bundle deflection was recorded in an atrial echo beat resulting from bundle-branch re-entry.

The post-premature driven (A1) impulse (not shown) was again conducted to the ventricles without a complete right bundle-branch block morphology.

In Fig. 2 the driving cycle length was decreased to 420 ms with the specific purpose of evaluating the effects of a faster basic rate on the production of atrial echoes. A2 (delivered at a coupling interval of 290 ms) reached the His bundle (H2), was blocked at the right bundle-branch, and reached the left ventricle with less delay than when driving cycle length was 670 ms. The shorter H2–V2 interval (125 ms) was attributed to the decrease in His-Purkinje refractoriness related to the decrease in driving cycle length. The impulse thereafter crossed the septum in a left to right direction, penetrated the right bundle-branch retrogradely, finally re-exciting the His bundle (H^-). An atrial echo beat did not occur as in Fig. 1 because H^- occurred at a moment in which both bypass tract and A-V node were 'effectively' refractory.

Because the driving cycle length was shorter than in Fig. 1 the post-premature A1 beat reached the right bundle-branch while this structure was still refractory from the concealed retrograde penetration of the preceding impulse. Hence this driven (A1) impulse was conducted to the ventricles with a complete right bundle-branch block pattern.

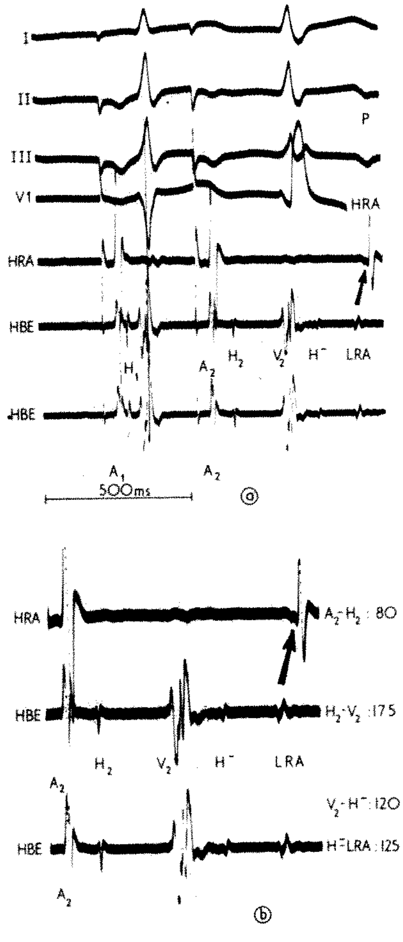

FIG. 1 *a) Atrial echo beat resulting from reciprocating mechanism involving the bundle-branches. Right atrium was driven from the vicinity of the inferior vena cava at a cycle length of 670 ms while a premature stimulus was delivered at a coupling interval of 330 ms. The first beat is the last of a series of eight consecutively driven (*A_1*) impulses. HRA = high right atrium. HBE = His bundle electrographic leads with interelectrode distances of 5 mm. LRA = retrograde low right atrial deflection recorded by the His bundle electrographic lead. *H^-* = retrograde His bundle deflection. Remaining abbreviations are conventional. b) Magnification of atrial echo beat. Reciprocating circuit was as follows: A2→H2→V2→*H^-*→LRA.*

Finally, the last driven A1 in Fig. 2 appeared later in the cycle, when the effective refractory period of the right bundle-branch had expired. It was therefore conducted with the same QRS morphology as the driven impulses.

Discussion

In most cases single atrial echoes result from re-entry within the A-V node, the determining factor being a critical A-H conduction delay (Goldreyer and Bigger, 1971; Goldreyer and Damato, 1971). But Lozano *et al.* (1973) studied one patient and Varghese *et al.* (1974) four patients in whom atrial echo beats appeared after critical His-Purkinje delay. Lozano *et al.* (1973) proposed that in their case a reciprocating mechanism involving the His bundle best explained the genesis of the arrhythmia.

TABLE *Duration and significance of conduction interval in atrial echo beat involving the bundle-branches*

A2–H2	(Atrio-His conduction time through the AV nodal bypass tract) = 80 ms*
H2-V2	(His to left ventricular conduction time through the left bundle system) = 175 ms
V2–H^-	(left to right transseptal time plus retrograde right bundle conduction time) = 120 ms
H^-–LRA	(retrograde AV nodal conduction time) = 125 ms†

* The slightly longer duration of this interval as compared with A1–H1 (45 ms) may be ascribed to conduction delay in the bypass tract. However, the bypass might have been only 'partial', the impulse being delayed in the part of the AV node that the supraventricular impulse had to traverse.

† Note that this interval was longer than both A1–H1 (45 ms) and A2–H2 (80 ms) intervals.

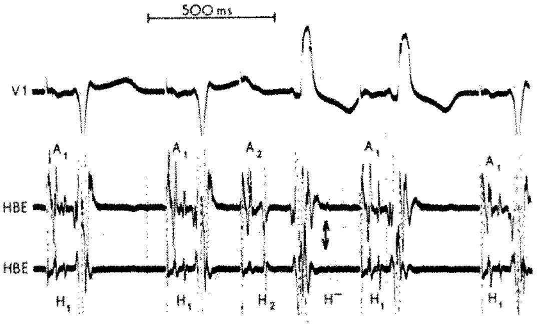

FIG. 2 *Retrograde activation of His bundle without atrial re-excitation. The driven rate was faster than in Fig. 1. Retrograde activation of the right branch (by the premature impulse) was responsible for the right bundle-branch pattern shown by the post-premature driven beat.*

On the other hand, Varghese *et al.* (1974) suggested that antegrade conduction of premature atrial beats was delayed in one bundle-branch and blocked in the contralateral branch, the impulse returning to the atria via the previously blocked bundle-branch or because of reciprocation within the conducting bundle.

But for bundle-branch re-entry to result in atrial echoes it is necessary that the His bundle be excited antegradely as well as retrogradely (Moe, Mendez, and Han, 1965). Since they could not detect a retrograde His bundle deflection in their tracings Varghese *et al.* (1974) postulated that it was lost within the ventricular electrogram recorded by the His bundle electrographic lead. The present study corroborates their assumptions. Besides it is also in keeping with the experimental studies of Moe *et al.* (1965), who first demonstrated that premature His bundle impulses could, after reaching the ventricles, activate the right bundle from its ventricular end to re-excite the His bundle.

Moreover, Fig. 2 shows that retrograde invasion of the right bundle-branch could be responsible for the right bundle-branch configuration of the post-premature atrial driven beats (Moe *et al.*, 1965; Cohen *et al.*, 1969). This phenomenon occurred only at the faster driven rates because the oncoming supraventricular impulse could reach the right bundle-branch during its effective refractory period. It is also in keeping with the findings of Spurrell, Krikler, and Sowton (1974), who presented evidence that the perpetuation of a bundle-branch pattern during reciprocating tachycardias could be due to concealed retrograde conduction of the affected bundle-branch.

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British Heart Journal, 1976, **38,** 304–306.

Diagnosis and successful surgical treatment of chronic constrictive uraemic pericarditis

H. R. Jenzer, E. Graedel, and A. Blumberg

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A case of chronic constrictive uraemic pericarditis successfully treated by pericardectomy is reported together with the pre- and postoperative haemodynamic data.

Uraemic pericarditis has become a common complication of chronic renal failure in patients maintained on haemodialysis. It usually responds to adequate haemodialysis together with pericardiocentesis or the creation of a pericardial window. Sometimes, however, chronic constrictive pericarditis develops, and this is likely to occur more often now that there are so many patients on long-term dialysis. We report here the pre- and postoperative haemodynamic data in such a case—the ninth case, we believe, to be described which has been successfully treated by pericardectomy.

Case report

In 1967 a 41-year-old man was found to have severe hypertension as a result of chronic renal disease. In 1970 bilateral nephrectomy was performed because of inadequate blood pressure control. The renal histology was that of chronic glomerulonephritis. Maintenance haemodialysis was started in hospital on 5 January 1970; the patient was transferred home on thrice-weekly haemodialysis in October 1970. In September 1973 he presented with chest pain, a friction rub, and a much enlarged cardiac silhouette (Fig. 1A). Acute uraemic pericarditis was diagnosed. It was suggested that dialysis should be done in the hospital in order to reduce the amount of anticoagulation needed, but the patient refused. He did not return until 15 January 1974, when he had an infection of the arteriovenous fistula. He stated that his previously moderate exertional dyspnoea had increased since December 1973. Moreover, he had noted that hypotension occurred when he attempted to reduce his weight during ultrafiltration dialysis.

On examination he had obvious neck vein distension, ascites, hepatomegaly (to 7 cm below the right costal margin), lower extremity oedema, blood pressure of 95 - 120/65 - 90 mmHg (12·6 - 16·0/8·7 - 12·0 kPa) without paradoxical pulse. Cardiac examination was unremarkable apart from a third heart sound. A chest *x*-ray film (Fig. 1B) showed the cardiac silhouette to be much smaller than it was during the episode of acute pericarditis 3 months before. The electrocardiogram showed ST depression and negative T waves, but no low voltage. In the course of several haemodialyses 7 kg of the fluid overload was removed, but the patient had a tendency toward hypotension while on dialysis.

The findings on right heart catheterization (see Table) accorded with the clinical diagnosis of chronic constrictive pericarditis. At operation on 19 February 1974 the pericardium was found to be leathery and 1 to 2 cm thick and the pericardial space was obliterated by fibrous tissue. Successful pericardectomy was performed. The patient's postoperative course was uncomplicated. He was discharged 11 days after the operation. Oedema and ascites gradually disappeared, neck vein distension and hepatomegaly decreased considerably, and heart size increased moderately. Haemodynamic findings confirmed the remarkable improvement (Table). When last seen the patient was continuing to do well.

Discussion

Uraemic pericarditis is common in patients with renal insufficiency but chronic constrictive uraemic pericarditis is rare. So far as we know, fewer than 20 cases have been reported and only 8 of these have had a successful pericardectomy (Nickey *et al.*, 1971; Comty, Cohen, and Shapiro, 1971; London *et al.*, 1971; Esmond, Lee, and Hernandez, 1971; Masbernard *et al.*, 1972; Young *et al.*, 1973). However, it is to be expected that, with the increasing use of maintenance haemodialysis, this complication will occur more often.

The diagnosis should be suspected when the following typical features are present. Distended

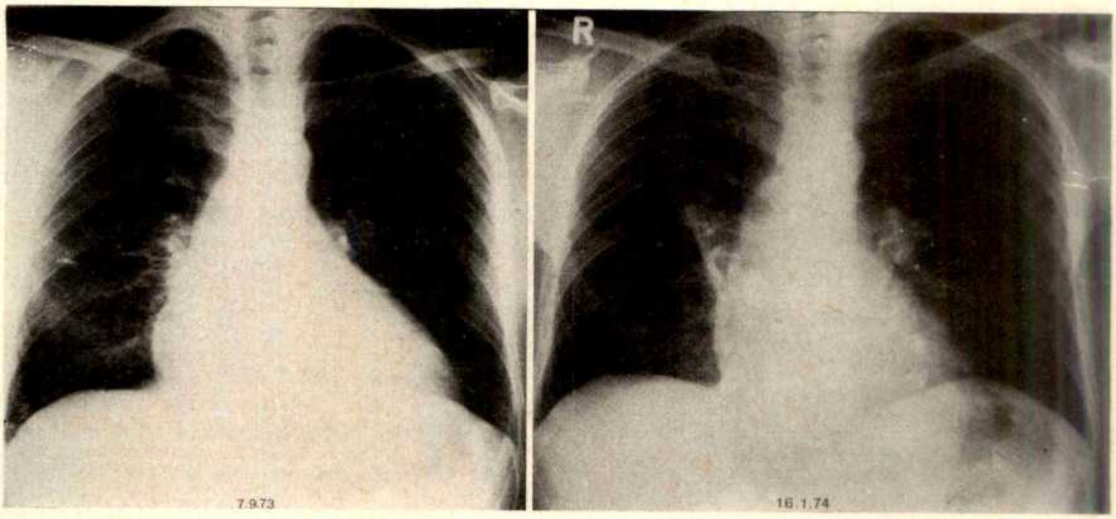

FIG. 1 *A) First chest radiograph (7.9.73) made at time of acute uraemic pericarditis shows enlarged cardiac silhouette. B) Second radiograph (16.1.74) shows reduction in heart size.*

neck veins, hepatomegaly, ascites, oedema, lowering of a previously raised blood pressure, and decrease in heart size. Cardiac catheterization in our case showed the characteristic haemodynamic changes with a pressure plateau in which the pulmonary wedge pressure, pulmonary artery diastolic pressure, right ventricular end-diastolic pressure, and mean right atrial pressure tended to be equal. An M pattern of the right atrial pressure pulse as well as an early diastolic dip in the right ventricle were also present. These haemodynamic abnormalities and clinical findings are not specific for the disorder, since a similar pressure pattern may be found in restrictive cardiomyopathies.

Chronic constrictive uraemic pericarditis seems to be a sequel to acute uraemic pericarditis. It is not clear why it develops in only a few cases and not in all. Pathogenetically the haemorrhagic nature of uraemic pericarditis is thought to be important. Incomplete resorption and secondary organization will then lead to the characteristic appearance of a spongy granulation tissue with organizing clot and residual fibrin (Reyman, 1969; Esmond *et al.*, 1971) but without calcification. Heparinization during dialysis probably contributes to pericardial bleeding. Therefore so-called regional heparinization should be performed. Unfortunately this was not possible in our case. Usually constriction develops within a few months, as in our patient (Delahaye *et al.*, 1964; Hager, 1965; Spaulding, 1967; Moraski and Bousvaros, 1969;Reyman, 1969; Brogard *et al.*, 1969; Weiss, Taw, and Hutchins, 1973). Only occasionally will it take more than a year (Lindsay, Crawley, and Callaway, 1970; London *et al.*, 1971).

The diagnosis should be evident from the physical findings, the chest *x*-ray examination, and additional right heart catheterization data. Since

TABLE *Pre- and postoperative haemodynamic data*

Site	*Pressure mmHg (kPa)**	
	Preoperative (31.1.74)	*Postoperative (12.6.74)*
Right atrium (mean)	17 (2·3)	5 (0·7)
Right ventricle (systolic/diastolic)	38/20 (5·1/2·7)	34/10 (4·5/1·3)
Pulmonary artery (systolic/diastolic; and mean)	42/20; 27 (5·6/2·7; 3·6)	27/9; 18 (3·6/1·2; 2·4)
Pulmonary artery wedge (mean)	20 (2·7)	7 (0·9)
Cardiac index l/min per m² (Fick method)	3·45	4·8

*Values in brackets in SI units.

this form of constrictive pericarditis is usually rapidly fatal prompt diagnosis and operation are mandatory. Without intervention 7 previously reported cases all died within 3 months (Delahaye *et al.*, 1964; Hager, 1965; Spaulding, 1967; Moraski and Bousvaros, 1969; Reyman, 1969; Brogard *et al.*, 1969; Lindsay *et al.*, 1970). Recent experience has shown that major surgery is feasible in patients on maintenance haemodialysis. The postoperative recovery of our patient (as well as that of several others) was rapid and uneventful, and the clinical improvement, corroborated by postoperative haemodynamic data, has been gratifying.

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British Heart Journal, 1976, **38**, 307–308.

Hydatid disease of the heart

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A case of hydatid cyst of the heart is described, in which the diagnosis was made at coronary angiography; a new angiographic sign is described.

Human infection with Echinococcus results from ingestion of ova excreted by infected dogs. Of these ova 15 per cent enter the systemic circulation having passed through the liver and lungs. Though ova occasionally reach the myocardium by way of the coronary circulation, hydatid disease of the heart is extremely rare, occurring in less than 2 per cent of all cases of echinococcosis.

Since the first case described by Dévé (1915), 133 cases have been reported. In our patient the diagnosis was made at coronary angiography and confirmed by a positive Casoni test and at operation. The diagnosis should be considered in patients who present with an abnormal heart shadow and who come from an area in which the disease is endemic.

Case report

The patient, a 23-year-old Iraqi student, complained of attacks of sharp, severe, left inframammary pain lasting for about two minutes during the preceding six months, occurring on average two or three times a week. The pain was unrelated to effort and the patient was able to lead an active life. The blood pressure was 140/90 mmHg (18·6/12·0 kPa) and the only abnormal sign in the cardiovascular system was an abnormal left ventricular im-

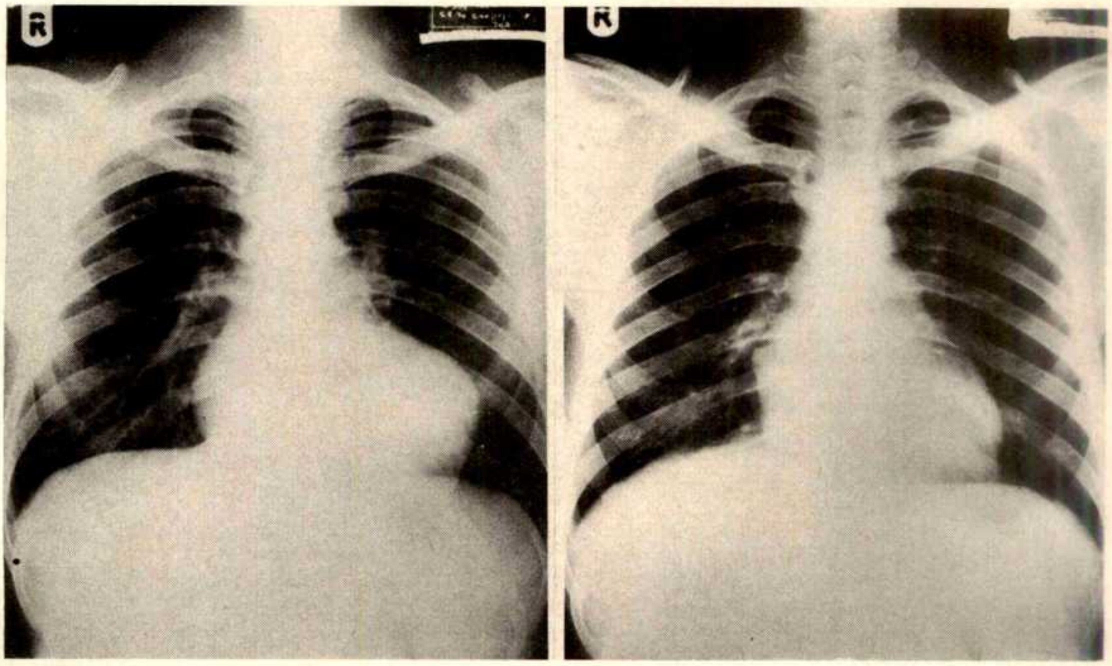

FIG. 1 *Chest x-ray before (left) and after (right) resection of hydatid cyst.*

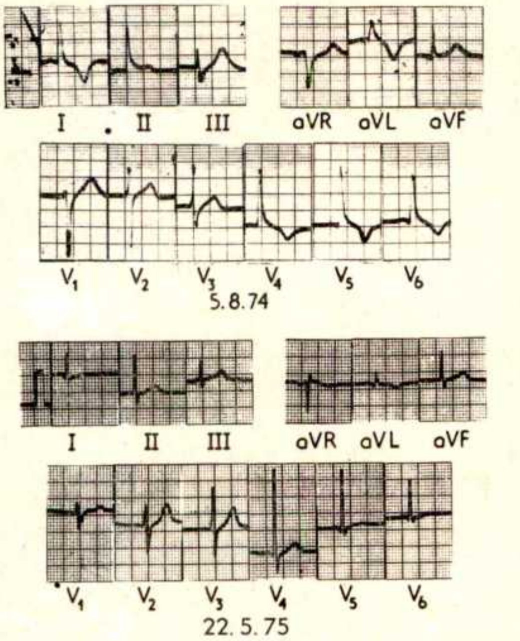

FIG. 2 *Electrocardiogram before and after resection of hydatid cyst.*

pulse. The chest *x*-ray (Fig. 1) showed enlargement of the heart (CTR 53%) and an abnormal shape of the heart shadow suggestive of left ventricular aneurysm. The electrocardiogram (Fig. 2) showed steep symmetrical T wave inversion in leads I, aVL, and V4-V6. Though the history was atypical and the electrocardiographic pattern unlike that of left ventricular aneurysm, it was decided to proceed to right and left heart catheterization and coronary angiography. Right and left heart pressures were normal and the left ventriculogram showed a filling defect on the anterosuperior surface of the ventricle. At coronary angiography the anterior descending branch of the left coronary artery and its large diagonal branch were displaced anteriorly and stretched around a large avascular mass in the wall of the left ventricle. The capillary phase of the angiogram showed a circular blush (Fig. 3). This large spherical mass in the heart led us to consider the diagnosis of hydatid cyst. It was then found that the patient not only lived in an area where the disease was endemic, but gave a history of contact with dogs throughout his childhood; the diagnosis was confirmed by a positive Casoni test, and the complement-fixation test was positive at a dilution of 1/64 (titres greater than 1/8 are significant).

Operation

The left ventricular myocardium was stretched thinly over a cystic mass about 6 cm in diameter, which extended into the left ventricular cavity and stretched the endocardium and anterior papillary muscle. Under cardiopulmonary bypass the heart was mobilized and the capsule of the cyst was exposed by a superficial incision.

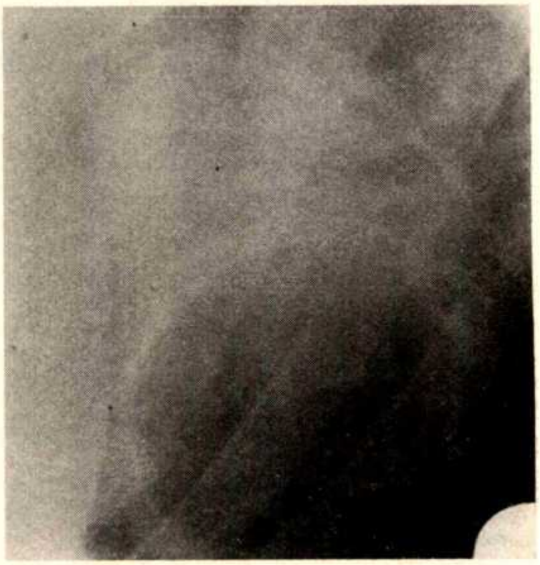

FIG. 3 *Left coronary angiogram—capillary phase. Right anterior oblique view.*

The myocardium was dissected free from the capsule by both sharp and blunt dissection and the cyst was delivered intact. The walls of the resulting cavity in the myocardium were approximated and the ventriculotomy was closed with a double row of sutures. The patient made an uneventful recovery.

At pathological examination the cyst was formed of a laminated outer layer and an inner germinal layer filled with a fluid in which innumerable scolices were suspended.

Seven months after operation the patient was well and symptom free. The chest *x*-ray and electrocardiogram had returned towards normal (Fig. 1 and 2).

Discussion

Although the diagnosis could have been made from a careful history and a positive Casoni test, it is quite likely that hydatid disease of the heart will be considered in other patients only after angiographic studies, as happened in this case. The circular capillary blush at coronary angiography may well prove to be a pathognomonic sign. Surgical removal can be rewarding.

I am grateful to Dr. M. Towers for permission to publish this case report. The patient was referred by Dr. R. P. K. Coe, and the operation was performed by Mr. Magdi Yacoub.

Reference

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Requests for reprints to Dr. M. E. Fawzy, Department of Cardiology, Harefield Hospital, Harefield, Middlesex.

Correspondence

British Heart Journal, 1976, **38**, 309–310.

Studies on innocent praecordial vibratory murmurs in children

Sir,

The tabulated standard errors of the mean (SEM) of the pre-ejection period (PEP) (papers by van der Hoeven *et al.*, *British Heart Journal* (1973), **38**, 669 and 679) imply remarkably similar standard deviations for each agesub group. This might suggest that the standard deviation of the 52 controls rather than that of each age subgroup was used to calculate the standard errors of the PEPs[1]. Because of the brevity of the summary, an explicit account of the significance test of the 15 innocent praecordial vibratory murmurs versus the 52 controls would permit a more critical review.

Calculations also show discrepancies between published and calculated values of the SEMs of both left ventricular ejection time (LVET) and PEP for both the 15 innocent praecordial vibratory murmurs and the 15 matched controls[2].

Most importantly, analysis of the published complete data[2] on the 15 innocent praecordial vibratory murmurs and 15 matched controls refutes the authors' claim of a significant difference at the level $P=0{\cdot}05$ between the PEPs. No significant difference at the 0·05 level was found using a paired t-test. An independent two-tailed t-test also revealed no significant difference at the 0·05 level. Only with a one-tailed test was significance found at the 0·05 level. However, the use and justification of a one-tailed test is not at all evident in the papers.

Therefore, we query the authors' statistical method from which significance was found in the matched control series as well as the unmatched series.

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and
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This letter was shown to G. M. A. van der Hoeven and his colleagues, who reply as follows:

Sir,

We appreciate the comments of Mr. Wong and colleagues on our papers on innocent praecordial vibratory murmur in children.

For the group of 85 normal children (Group A), whose ages are between 1 and 20 years, the calculated relation between pre-ejection period (PEP) and heart rate (HR) is

$\mathrm{PEP}=-0{\cdot}33\mathrm{HR}+113$ (ms) (Eq. 1)

Syx[1] = SD (PEPc) = 11·7.

Using this we found PEP values corrected for heart rate

$\mathrm{PEPc}=\mathrm{PEP}+0{\cdot}33\mathrm{HR}$ (Eq. 2)

We used the Syx = 11·7 of the total group to calculate the SEM's for each subgroup, despite smaller actual standard deviations of the 4 subgroups. The SD for PEP values and the SD for PEPc values were for the four subgroups resp.:

10·4, 10·1, 11·6, 7·07 and 9·3, 8·9, 11·5, 6·6.

The rationale for taking the larger value was to take into account possible future interobserver differences and the fact that each subgroup consists only of a very small number of subjects. We regret not having mentioned these reasons explicitly in our papers.

In the second paper (2), we compared the PEP values of 15 children with innocent praecordial vibratory murmurs and a subgroup of 52 normal children, between 1 and 10 years, taken from the total group A. The regression equation for this subgroup B is:

$\mathrm{PEP}=-0{\cdot}32\mathrm{HR}+110$ (ms) Syx = 9·0.

From this group B, a second subgroup of 15 children was taken to serve as an age matched control group for the 15 children with innocent praecordial vibratory murmurs.

The difference in PEP between children without and with an innocent praecordial vibratory murmur is calculated using PEPc (Eq. 2).

The heart rate corrected PEP values and the standard deviations for all groups are:

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[1] Table 1, *British Heart Journal*, **35**, p. 673.

[2] Table 1, *British Heart Journal*, **35**, p. 682.

[1] Syx = sample standard deviation from regression.

	Age	*Mean age*	*No.*	*PEPc*	*SD (PEPc)*
Group A	1–20	9·1	85	113·2	11·7
Group B	1–10	6·0	52	110·3	9·04
Controls	3–10	6·2	15	107·9	8·63
IPVM	3–10	5·9	15	100·6	11·94

IPVM—Innocent praecordial vibratory murmurs.

Using the two-tailed Student's t-test for independent samples the values of PEPc for the children with innocent praecordial vibratory murmurs are significantly different with respect to the PEPc value of group B ($P < 0{\cdot}01$).

We concluded that children with innocent praecordial murmurs have a shorter PEP than children without one. Knowing this, a one-tailed Student t-test may be used to compare the controls and the innocent praecordial vibratory murmurs. The PEPc of the children with innocent praecordial vibratory murmurs is significantly shorter than matched controls ($P < 0{\cdot}05$).

Using a non-parametric method (Wilcoxon signed rank test) the same conclusion may be drawn.

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Successful aortic valve replacement for aortic regurgitation associated with osteogenesis imperfecta

Sir:

The paper by Weisinger *et al.* (*British Heart Journal,* 1975, **37**, 475) is similar to a published report by me (Pijoan de Beristain, 1973). This paper described a mother and son with aortic regurgitation associated with osteogenesis imperfecta. The mother died in 1960 but the son was operated on successfully in 1966 and is still alive and doing well. The surgeon's description of the aortic wall was similar to that of Weisinger *et al.* and also to that found in Marfan's disease.

I believe that in every case of isolated aortic regurgitation the stigmata of Marfan's syndrome and osteogenesis imperfecta must be looked for.

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Spain.

Reference

Pijoan de Beristain, C. (1973). Association of aortic insufficiency with osteogenesis imperfecta in 2 members of the same family. *Revista Española de Cardiologia,* **26**, 405.

British Heart Journal (1976), **38**, 311–321

Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held in London on 13 and 14 November 1975. At the private business meeting the President, J. F. GOODWIN, was in the Chair. For the scientific meeting P. H. DAVISON was in the Chair. The three finalists in the competition for the Young Research Workers Prize were T. Pickering, P. A. Poole-Wilson, and K. M. Taylor. The Prize was won by T. Pickering. A Joint Symposium with the Cardiac Muscle Research Group was held with E. M. VAUGHAN-WILLIAMS in the Chair.

At the Dinner a presentation on behalf of the Society was made by the President to the retiring Executive Secretary, Miss E. G. North. Expressions of appreciation of Miss North's sterling work for the Society were made by Dr. J. P. Mounsey and Professor J. P. Shillingford.

Abstracts of Papers

Paroxysmal re-entry sinus tachycardia

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Paroxysmal re-entry tachycardia may affect the sinoatrial node (PRST): we have carried out intracardiac studies on 7 patients. The presentation was unrelated to PRST in 5 (that of sinoatrial disease, 4; WPW syndrome with paroxysmal tachycardia, 1); in 2 patients with palpitation, electrocardiograms suggested PRST. In 4, sustained PRST could be initiated and terminated by single critically-timed right atrial premature beats over a definite 're-entry zone'; in 3, PRST was poorly sustained, the re-entry zone small, and initiation or termination less reproducible. Rates during PRST ranged from 88 to 156. In all the P wave configuration and atrial activation sequence were virtually identical in PRST and sinus rhythm, high right atrial deflections differing slightly from those of sinus beats in 5. Verapamil prevented re-entry in 2 with sustained PRST and was ineffective in 2 who responded to ajmaline. Carotid sinus massage terminated PRST in 2, prolonged the cycle length without termination in 2, and had no effect in 1.

Sinus node re-entry deserves consideration as a cause of inappropriate sinus tachycardia and can be confirmed electrophysiologically.

Torsade de pointes; an atypical ventricular tachycardia

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A typical ventricular tachycardia, often self-limiting, in which, characteristically, the QRS axis fluctuates, has been called 'torsade de pointes'. We have studied 15 patients with this disorder, and have found it as a complication of sinoatrial and atrioventricular block, hypokalaemia, and cardiac ischaemia, and as a toxic effect of various antiarrhythmic agents, phenothiazines, and tricyclic antidepressants. Similar appearances were also seen in one member of a family suffering from hereditary prolongation of the QT interval associated with sudden death. In a further 4 patients, it was induced during cardiac stimulation studies.

This arrhythmia appears to be caused by re-entry rather than enhanced ectopic activity. It can usually be recognized from the surface electrocardiograms, but in doubtful cases the diagnosis may be supported by recognition of possible underlying causes. While some cases are of long duration, it is not benign: we have observed the development of ventricular fibrillation in 5 of our cases. Antiarrhythmic agents usually effective in ventricular tachycardia are unhelpful and may be dangerous; cardioversion, rapid right atrial pacing, or intravenous isoprenaline may be needed, and correction of underlying factors (where possible) is of fundamental importance.

Clinical electrophysiological effects of mexiletine and its mechanism of antidysrhythmic action

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King's College Hospital, London SE5

Mexiletine 2 to 3 mg/kg body weight was given intravenously over 10 minutes. The blood levels at the beginning ($0{\cdot}98\pm0{\cdot}1$ µg/ml) and end ($0{\cdot}97\pm0{\cdot}09$ µg/ml) of the electrophysiological recordings were within the antidysrhythmic therapeutic range (0·5 to 1·5 µg/ml).

No consistent effects were observed on the refractory period of the atrium or atrioventricular node. Significantly the relative refractory period of the His Purkinje system was shortened by mexiletine in all 9 patients in whom it could be measured, from a control value of 437 ± 11 to 398 ± 8 ms ($P < 0{\cdot}05$). No significant changes occurred in sinus rate, atrioventricular or His Purkinje conduction time.

This study, therefore, shows that mexiletine has important clinical electrophysiological differences compared with other Class 1 agents, e.g. quinidine, procainamide, and the beta-adrenergic blocking agents. The observed effects on refractoriness in the His Purkinje system may explain the efficacy of mexiletine in re-entrant ventricular arrhythmias and indicates that its use should be relatively safe in patients with infra-His conduction disturbances.

Echocardiography in infective endocarditis

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Valvar vegetations of infective endocarditis have been shown by echocardiography. Six patients were investigated at the National Heart Hospital: 5 showed massive vegetations on the aortic valve and one showed a massive vegetation on the mitral valve. The aortic vegetations were so prominent as to fill the aortic root in diastole, and in 3 cases prolapsed into the left ventricular outflow tract; the mitral vegetations filled the mitral orifice in diastole. Echocardiography also showed thickening of the anterior sinus of Valsalva in one aortic case which proved to be an aneurysm.

The infecting organism was bacterial and different in each case. All 6 patients proceeded to valvar replacement; there were no deaths and the echocardiographic findings were confirmed in each case. The vegetations were florid and friable. The indications for surgery were failure to control infection despite adequate antimicrobial therapy with *in vitro* control in 3, and intractable heart failure in 3. We conclude that demonstration of massive vegetations by echocardiography indicates that the lesions are so severe as to preclude successful medical treatment and early valve replacement is indicated; furthermore cardiac catheterization before surgery may be hazardous.

Within-patient test of reliability of echocardiographic left ventricular dimensions and cavity and wall volume estimation

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This test is based on the incompressibility of myocardium which dictates that left ventricular wall volume remains constant throughout the cardiac cycle.

The volumes occupied by the left ventricular cavity, by ventricular cavity plus wall, and hence by ventricular wall alone, can be estimated from echocardiographic measurements of wall thickness (W) and cavity dimension (D). A discrepancy between wall volume estimates at end-systole and end-diastole indicates that either the dimensions are unreliable or that the assumptions of ventricular geometry on which the volume calculations are based are incorrect.

Forty patients were studied. Wall volumes were determined by assuming an ellipsoid shape $(4/3\pi((W+D/2)^2(W+L)—(D/2)^2L)$; the semimajor axis (L) being predicted from a regression equation relating angiographic and ultrasound dimensions), and also by the cube method $((2W+D)^3—D^3)$.

Using the ellipsoid formula, values for wall volume ranged from 92 to 719 ml; end-systolic and end-diastolic wall volumes correlated closely (r=0·95, mean difference=6·7±1·0(SEM)%), supporting the reliability of the echocardiographic measurements. In the 7 patients with very large end-diastolic cavity dimensions (6·5–8·6 cm), however, correlation was poor (mean difference=18·5±2·7(SEM)%). Using the cube method, wall volumes were greater (102—986 ml) but correlation was similar (r×0·91, mean difference=7·2±1·1(SEM)%).

This test can be useful for assessing the reliability of echocardiographic ventricular measurements in individual subjects.

Description of segmental wall motion abnormalities in patients with coronary artery disease

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Forty patients being investigated for chest pain were studied at routine cardiac catheterization by performing 3 sequential left ventriculograms at rest, after pacing and after nitroglycerine.

Using single plane RAO angiograms and dividing the ventricle into 8 segments based on a conventional long axis measurement, normal values for systolic segment motion have been defined in 10 patients without coronary disease. The change in segment areas between end diastole and peak systole varied from 45 per cent (SD=11%) in the posterior wall of the left ventricle to 65 per cent (SD×10%) on the high anterior wall and were reproducible between sequential studies.

Patients with coronary artery disease who developed angina during pacing showed changes in systolic wall motion in territories of poor coronary supply which were reversed by nitroglycerine. Assessment of changes in wall motion by long axis measurement depends on the position of the apex which may alter during ischaemia, and a comparison between conventional segmental description and a technique depending upon radial measurements from the centre of gravity of the single plane view was presented.

Heart scanning with ^{99}Tc^{m} stannous pyrophosphate

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^{99}Tc^{m} stannous pyrophosphate is a radioactive marker which is cheap, safe, and generally available. It labels freshly damaged but not normal or scarred myocardium, thus giving a positive scan in recent infarction.

Using simple mobile apparatus, heart scans have been obtained at the bedside in 52 patients. The anterior scan was the most useful, an abnormal result being indicated by asymmetry about the sternum.

In acute myocardial infarction, positive scans were found between 17 hours and 18 days after the onset of symptoms. When the infarction was definite on other grounds, the scan was positive in all of 15 patients, when likely in 12 of 16, and when doubtful in 9 of 21 patients.

Heart scanning with ^{99}Tc^{m} stannous pyrophosphate is useful in the assessment of suspected myocardial infarction. Preliminary studies suggest that it is reliable, sensitive, and of particular value when previous damage makes electrocardiographic interpretation difficult, and when raised enzyme levels cannot be attributed with confidence to the heart.

Prognosis of early myocardial ischaemia

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A simple screening examination was made of 16 016 male civil servants aged 40 to 59 and included a standardized chest pain questionnaire, electrocardiography, and assessment of the main coronary risk factors. In the ensuing 5 years, 181 of these men died of coronary heart disease. 'Angina', with a prevalence of 4·3 per cent, carried a mortality ratio of 5·4 and predicted 19 per cent of these deaths. For a history of 'pain of possible infarction' the prevalence was 6·5 per cent and mortality ratio 5·8; 29 per cent of deaths from coronary heart disease were predicted. 5·6 per cent showed electrocardiographic abnormalities suggesting ischaemia, with a mortality ratio of 7·0 and prediction of 29 per cent of deaths. Altogether 14·3 per cent of men were positive to one or other of these indices of suspect ischaemia; this combined category carried a mortality ratio of 6·4 and predicted more than half of all the 5-year deaths from coronary heart disease. Among the men with suspect ischaemia the predictive significance of blood pressure, plasma cholesterol, glucose tolerance, overweight, and cigarette smoking seemed to be as great as in their contemporaries without ischaemia.

These findings were discussed in relation to policy on the detection and management of early myocardial ischaemia.

Fibrinolytic activity and risk factors for coronary heart disease

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The response of the fibrinolytic system to stress (venous occlusion) has been examined in healthy middle-aged men who had consistently shown either high or low resting fibrinolytic activity (FA) on repeated studies over several years. There was a close relation between resting FA and the response to venous occlusion, though subjects with low resting FA showed considerable variation in response. The group with high resting FA and a uniformly good response to stress had significantly lower levels of plasma cholesterol and triglycerides, lower Quetelet's index, lesser skinfold thickness, and lower blood pressure. This group also included more non-smokers and more physically active subjects. Subjects who had never smoked clustered in the area of high response to stress. When the low resting activity group was divided into those with low or high response to stress, differences in several risk factors were present and showed an interesting trend.

Hypotheses relating the risk factors to atherosclerosis and to coronary heart disease are presented and it is suggested that the response of the fibrinolytic system to stress may provide an index of atherosclerosis.

Comparison of antihypertensive effectiveness of beta-adrenoceptor antagonists with different pharmacological properties

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There is little information on the comparative antihypertensive activity of beta-adrenoceptor antagonists with different spectra of ancillary pharmacological properties. Both the immediate and the long-term blood pressure lowering activity of propranolol, oxprenolol, practolol, tolamolol, and metoprolol were, therefore, compared at rest and during treadmill walking in patients with stable, uncomplicated essential hypertension (diastolic pressure 110 to 120 mmHg (14·6 to 16·0 kPa)). The trial was designed as a randomized double-blind cross-over study with particular respect to dose-response relations.

With all drugs there was a similar significant reduction in blood pressure within an hour, which was maintained for over 8 hours, greater for systolic than diastolic pressure and greatest during exertion. There was a significant relation between the reductions in systolic pressure and the logarithm of dose of each drug. These effects were enhanced during long-term treatment where again there was a logarithmic relation between dose and blood pressure lowering activity.

It is concluded that the blood pressure lowering activity of beta-receptor blocking drugs is greatest on systolic pressure, greatest during exertion, enhanced by continuous treatment, and independent of their ancillary pharmacological properties.

Effect of selective and non-selective beta-blockade on coronary circulation in man

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Eight patients undergoing cardiac catheterization for suspected coronary artery disease were studied. Myocardial blood flow was measured using a Ganz thermodilution catheter placed in the coronary sinus. Systemic arterial pressure and arterial blood samples were obtained from a brachial artery cannula.

Myocardial arterial and coronary sinus blood samples, systemic blood pressure, and heart rate were obtained before and during pacing to angina threshold, ST–T changes or 150 beats/minute. After the administration of 0·1 mg/kg propranolol (4 patients) or atenolol (4 patients) measurements were repeated at the achieved heart rate and at the heart rate immediately before drug administration. The heart was then rapidly paced to the same rate as previously.

Neither the non-selective beta-blocker propranolol, nor the relatively selective atenolol produced significant coronary vasoconstriction. Changes in coronary resistance were related to changes in myocardial oxygen consumption, myocardial oxygen extraction remaining unchanged.

Thyroid stimulating hormone levels in atrial dysrhythmias

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A study of 80 clinically euthyroid patients who had cardiac disease and/or atrial dysrhythmias has been made, in which the level of thyroid stimulating hormone (TSH) and the response to thyrotrophin (TRH) has been estimated in conjunction with clinical assessment and conventional thyroid function tests, to detect occult thyroid disease. Forty of the patients had established atrial fibrillation, 20 others had paroxysmal atrial dysrhythmia, and 20 more had heart disease without dysrhythmia.

Although 3 patients were found to have true hyperthyroidism, the overall results were contrary to what had been expected. Twelve cases were disclosed (10 with chronic atrial fibrillation, 2 with paroxysmal dysrhythmia), where the basal TSH level and its response to TRH was exaggerated, despite the absence of thyroid hypofunction as judged clinically or from the standard tests of thyroid function. No patient from the group with heart disease alone had raised TSH levels. It is apparent that any patient with established atrial fibrillation from any cause is likely to have abnormally high TSH levels, both basally and after TRH stimulation, compared with those with paroxysmal dysrhythmia or those with heart disease but without rhythm changes. Two possible explanations were discussed: i) that thyroid autoimmune disorder may be closely linked to atrial muscle damage; ii) that circulating metabolities of thyroid hormones partially inhibit thyroid function but affect cardiac muscle excitability.

New observations on systolic anterior motion of mitral valve leaflets in hypertrophic cardiomyopathy

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Eighteen patients with hypertrophic cardiomyopathy were scanned with the Siemens 'Vidoson', a real-time dynamic B-scanner, only recently introduced for routine two-dimensional cine-echocardiography. The diagnosis was proven by angiocardiography and high fidelity pressure measurements in 12 patients, and in the remainder was made by both clinical and M-scan echocardiographic examinations. This study shows that the two-dimensional cross-sectional display of the Siemens 'Vidoson' is superior to the M-scan technique for the diagnosis of hypertrophic cardiomyopathy, since the latter is dependent on beam direction.

Furthermore, real-time scanning, being extremely rapid, allows true anatomical relation within the heart to be seen, and quantitative assessments of the exact location and extent of the septal bulge to be made.

In particular, the motion of the prominent hypertrophied papillary muscles is easily seen. Evidence is presented to support the contention that the characteristic systolic anterior motion is caused by an exaggerated upward motion of the chordae tendineae, brought about by synchronous displacement of the rigid left ventricular posterior wall and attached papillary muscles in systole.

The results suggest that the systolic anterior motion is produced by reflection of the chordae tendineae, which traverse the sound beam at certain phases of the cardiac cycle, rather than by the tips of the mitral leaflets themselves. A typical example was illustrated by a cine film.

Arterial oxygen tension and response to oxygen breathing in differential diagnosis of congenital heart disease in infancy

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Arterial oxygen tension was measured from radial artery samples in 285 infants referred for cardiological investigation. Values obtained during air breathing in infants with congenital heart disease showed considerable overlap between 'cyanotic' and 'acyanotic' groups and are of limited diagnostic use. In contrast, values obtained while breathing oxygen in concentrations of over 80 per cent, measured in 182 infants, allowed clear differentiation between these groups.

All infants with 'acyanotic' but only 2 of 109 with 'cyanotic' lesions achieved an arterial oxygen tension of more than 150 mmHg (20·0 kPa). In the 'cyanotic' group, the response to oxygen breathing was significantly greater with common mixing situations and the hypoplastic left heart syndrome than with either pulmonary outflow tract obstruction or transposition of the great arteries. Of 23 infants with primary lung disease, suspected initially to have cyanotic congenital heart disease, 7 achieved arterial oxygen tensions of more than 150 mmHg (20·0 kPa) during oxygen breathing and, on this basis, cardiac catheterization was not performed.

We, therefore, submit that measurements of the arterial oxygen tension while breathing high concentrations of oxygen should be routinely performed in the initial assessment of sick infants with suspected congenital heart disease.

Thromboembolic complications after aortic valve replacement: comparative study

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The long-term results after aortic valve replacement with either a Starr Edwards silastic ball prosthesis (model 2320, cloth covered cage), or Bjork Shiley tilting disc prosthesis, have been analysed, with particular attention to complications or death as a result of thrombosis of the valve or embolism from it. The incidence of thromboembolic complications in these two groups was compared with that of a similar sized group of consecutive patients who had undergone homograft replacement of the aortic valve. Most patients undergoing Starr valve replacement were treated for about three months with phenindione which was subsequently discontinued. On the other hand, patients in the Björk Shiley group received no postoperative anticoagulation, and no anticoagulation was used with the homograft group.

The incidence of thromboembolism in the homograft group was negligible. A small number of patients with Starr valves had serious thromboembolic complications. However, non-anticoagulated patients with the Björk prosthesis in the aortic position had an unacceptably high incidence of emboli and/or valve thrombosis. This incidence was so high that we have discontinued this study group and anticoagulated all patients with Bjork Shiley prosthesis.

Myocardial infarction in patients undergoing coronary artery bypass grafting

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The incidence of perioperative myocardial infarction in 250 consecutive patients undergoing coronary bypass grafting was studied. Patients who had additional procedures (excision of aneurysms or infarcts or valve replacement) were excluded from the study. Myocardial infarction was diagnosed by set electrocardiographic criteria. Sixteen patients (8%) developed evidence of new myocardial infarction. Of these, 1 died early and 1 late. The site of the infarct was in the territory of a grafted vessel in all patients.

Cardiac enzymes, including the cardiospecific isoenzyme CK.MB, were evaluated in 50 patients. These were abnormally high in 8 patients (16%).

Sixteen patients with perioperative infarction were followed up for periods of up to 5 years. All patients showed symptomatic improvement.

Repeat coronary and left ventricular angiography showed patent grafts to the infarcted area in 15 and occluded in 3 (a patency rate of 83%). The infarct did not influence left ventricular ejection fraction in 14 and produced reduction in the other 4. This was not related to graft patency.

It is concluded that perioperative infarction is not related to graft patency and influences left ventricular function in a proportion of cases.

Currently we are investigating the use of beta-blockers and hypotensive agents during and immediately after operation to reduce the incidence and severity of this complication.

The watershed: a factor in coronary vein graft occlusion

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Of 215 patients with one or more aortocoronary saphenous vein grafts, all 16 survivors with a poor clinical result and 34 others with a good result were investigated by angiography to determine graft patency, half within one month of operation and half after a longer interval. Seventy per cent of the grafts were patent but the patency rate of grafts inserted into arteries with a proximal occlusion was found to be significantly higher ($P < 0{\cdot}05$) compared with those inserted into arteries with a proximal stenosis; this difference was greater ($P < 0{\cdot}025$) in those investigated after more than one month. A watershed was shown at the anastomosis in one patient, with a graft inserted into a non-occluded artery: the distal run-off appeared good, but reflux of contrast up the coronary artery into the aorta occurred when injecting into the graft, and vice versa. It is suggested that this watershed is operative to a minor degree in all grafts inserted into non-occluded arteries and, by causing stasis at the anastomosis, is the explanation for the higher incidence of graft occlusion in this group. Ligation of the coronary artery proximal to the anastomosis may, therefore, be necessary to achieve the highest patency rate.

Total correction of tetralogy of Fallot postoperative haemodynamic assessment

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Postoperative haemodynamic evaluation was performed on 15 patients approximately 11 years after total intracardiac repair of Fallot's tetralogy. At the time of the postoperative study all the subjects were asymptomatic.

The cardiac output and right heart pressures were measured at rest and after 5 minutes' sub-maximal exercise on a bicycle ergometer. It was shown that the degree of residual obstruction of the right ventricular outflow tract was slight; the RV-PA systolic gradient exceeded 20 mmHg (2·7 kPa) at rest in only 3 patients. The mean cardiac index at rest was 5·4 l/min per m^2 which increased to 8·3 l/min per m^2 during exercise. The response of the cardiac output to exercise was subnormal in one patient but either normal or supranormal in the others. Pulmonary regurgitation was present in 8 of the 15 patients but these patients showed no significant difference in their cardiac function compared to those with competent pulmonary valves.

Six of the patients in the present study had cardiac catheterizations performed 1 to 4 years after operation. The later study shows remarkably little change in their haemodynamic status. These results are encouraging but the long-term effects of the right ventricular pressure and volume overload are unknown.

Homograft reconstruction of right ventricular outflow tract in pulmonary atresia—late results

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The 24 consecutive survivors of right ventricular outflow reconstruction with an aortic homograft for pulmonary atresia and extreme Fallot and failed correction of Fallot have been studied 3 to 10 years after operation. There have been no late deaths, no haemolysis of thromboembolism, and no patients have been lost to follow-up. One patient, the first patient operated on aged 9 years, had reoperation after 9½ years for right ventricular obstruction which had occurred because the homograft was the smallest used (Size 1) and had not grown with the boy; right ventricular failure had occurred in the eighth postoperative year.

All patients lead normal asymptomatic lives and two had uncomplicated pregnancies, delivering normal children. Pulmonary regurgitation was present in 70 per cent and did not progress. Pulmonary valve closure (P_2), from the aortic homograft, remained clear, despite radiological appearances of calcium in the graft aortic wall in 22 patients.

Cardiac catheterization was performed in 21 and repeated in 10. Resting gradients across the graft were 5 to 35 mmHg (0·7 to 4·7 kPa) and did not increase except in the first patient.

The difference in these results and some transatlantic reports may be explained by different methods of sterilization and selection of patients. From this study we see no reason to abandon the use of homografts for reconstruction of the right ventricular outflow tract in cyanotic congenital heart disease.

Intra-aortic balloon assistance in cardiogenic shock after myocardial infarction or cardiac surgery

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Sixty-five patients with cardiogenic shock were referred for consideration for intra-aortic balloon assist (IABA). Fifty-two were accepted, 30 patients with myocardial infarction and 22 patients who could not be weaned off cardiopulmonary bypass. Twenty-one of the accepted patients were referred from the region.

Criteria for acceptance after myocardial infarction were a systolic arterial pressure of <90 mmHg (12·0 kPa) persisting for >2 hours, with a urine output <20 ml/hour, and cool peripheries or mental clouding. In 8 of the 30 patients death occurred within one hour and before IABA could be established. In the 22 patients established on IABA, the initial mean arterial pressures were 80±2·5 mmHg (10·6±0·4 kPa) systolic, 66±2 mmHg (8·8±0·3 kPa) mean, and 55±2 mmHg (7·3±0·3 kPa) diastolic. Sixteen patients showed clear haemodynamic improvement during IABA, of whom 5 survived to leave hospital; a hospital survival of 23 per cent.

Appropriate early angiography and coronary artery surgery on IABA could probably further improve this survival rate. The study clearly showed in 15 patients that IABA could be satisfactorily established in a peripheral hospital, continuing during transport and subsequent coronary angiography. The gain in survival from cardiogenic shock complicating myocardial infarction should be compared with the hospital survival of 6 from 16 (38%) cardiac surgical patients who could not initially be weaned from cardiopulmonary bypass.

'Isolated' pulmonary valve stenosis: a possible misnomer

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Histological studies have been made on the myocardium of both ventricles, the coronary arteries, and the ascending aorta in 25 specimens with 'isolated' pulmonary valve stenosis from children aged 6 days to 9 years. Serious abnormalities in these areas have been found in 23. Myocardial infarction and dysplasia in both ventricles was common and widespread obstructive changes in the coronary arteries were found in 17. The media of the ascending aorta were abnormal in 12.

Clinical scrutiny of a different series of 10 children aged 8 months to 3 years after open pulmonary valvotomy for simple pulmonary valve stenosis showed examples of unexplained pulmonary oedema, persistent low cardiac output, subsequent left ventricular enlargement, and systolic hypertension.

In an older group of 43 patients aged 4 to 20 years who had pulmonary valvotomy, there were 7 who developed obvious left-sided problems for no apparent reason. Two developed the features of classical obstructive cardiomyopathy 6 and 8 years later.

It is suggested that some of the unexpected clinical features in pulmonary valve stenosis may be explained by the pathological abnormalities. This also suggests that pulmonary valve stenosis may be on occasion part of a more widespread cardiovascular disease. This should be suspected in infants with severe pulmonary valve stenosis, those who present with thickened tricuspid valves, and in children with stigmata of congenital abnormalities outside the cardiovascular system.

Experience with an extractable aortic flow probe after open heart surgery

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Precise, sensitive haemodynamic monitoring is essential in the intensive care period after cardiac surgery. With the innovation of the Williams-Barefoot extractable electromagnetic aortic flow probe, a system has been developed for post-cardiac surgical monitoring which provides continuous on-line information concerning aortic flow, together with pressure measurements as available in most conventional systems.

The probe is positioned around the aorta during open heart surgery, and is easily removed by cutting an external snare and gentle traction after the intensive haemodynamic monitoring period. The probe has been left *in situ* for up to 8 days. The system provides a continuous display of cardiac output, stroke volume, stroke work, an index of peripheral resistance, and routine pressure values. It also has play-back facilities for measurement of the acceleration of aortic flow, cardiac power, and other indices of myocardial function. This system is described and its use illustrated in the assessment of dobutamine, a new inotropic agent, which possesses less chronotropic activity for a given inotropic action in animal experiments.

In 14 patients, dobutamine and isoprenaline were randomly administered in incremental doses to patients after cardiac surgery. Dobutamine, when compared with isoprenaline, produced less increase in heart rate, a modest rise in both systolic and diastolic pressure at comparable inotropic levels, but cardiac output and myocardial metabolic studies did not reveal any particular myocardial economic benefit with dobutamine in these patients.

The significance of these findings in relation to the use of inotropic agents, and monitoring techniques after open heart surgery will be discussed.

Mustard operation in patients with pulmonary vascular disease

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A contraindication to the Mustard operation for transposition of the great arteries has been high pulmonary vascular resistance (PVR). Since 1973 we have adopted Lindesmith's policy of a 'palliative' Mustard operation for patients with transposition of the great arteries and ventricular septal defect in whom the pulmonary vascular assistance is high. The Mustard operation is performed but the ventricular septal defect is left open so that it may act as a vent should the pulmonary vascular resistance increase further. Twelve 'palliative' Mustard operations have been performed in children whose ages ranged from 3 to 14 years (mean 7·3 years). The haemoglobin ranged from 14 to 23·5 g/dl (mean 19·6 g/dl), and haematocrit 41 to 81 per cent (mean 62%). All patients survived the operation and improved; the postoperative arterial oxygen saturation ranging between 80 and 94 per cent (mean 89%).

The 'palliative' Mustard is strongly recommended in patients with transposition of the great arteries and ventricular septal defect in whom diagnosis and treatment has not been instituted before pulmonary vascular assistance becomes severely raised. This concept has been extended successfully to include 1 patient with transposition of the great arteries and an intact ventricular septum in whom the Mustard operation was performed and a ventricular septal defect created in the lower part of the muscular septum.

Tricuspid atresia—morphology and classification

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Eighty-six hearts have been examined in which the morphological tricuspid valve was either absent or imperforate. Five specimens possessed an imperforate valve situated between the right atrium and a poorly formed right ventricle. The right ventricle contained tension apparatus of the valve. The remaining 81 hearts all had the ventricular morphology of 'primitive ventricle', 78 possessing an outlet chamber and 3 being examples of tricuspid atresia in primitive ventricle without outlet chamber. All the primitive ventricular hearts were from solitus individuals and 75 had atrioventricular concordance. In the 6 examples with atrioventricular discordance, the left atrium was blind-ending and a mitral valve was placed between the right atrium and the primitive ventricle. The outlet chamber was left sided. Striking variation was noted in ventriculo-arterial relations. Fifty-four hearts had normally related great arteries and 18 had transposed arteries. Three examples of anatomically corrected malposition, one example of double outlet malposition from the outlet chamber, and 5 examples of single arterial trunk were observed. The single trunk was a common truncus in one instance and the aorta in the remainder. Pulmonary stenosis was encountered in 40 hearts. It was most frequently the result of a constrictive bulboventricular foramen in the presence of normally related great arteries. A constrictive foramen in association with transposed arteries was seen 7 times with aortic isthmal hypoplasia. The findings emphasize the necessity of adopting a segmental approach in order to describe adequately hearts with tricuspid atresia.

Congenital aortic valve disease with rupture of mitral chordae tendineae

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A new clinical entity is described in which free aortic regurgitation from congenital aortic valve disease causes rupture of the chordae to the anterior leaflet of the mitral valve. Comparing these patients with those who rupture mitral chordae in association with rheumatic heart disease and patients with spontaneous chordal rupture, differences were evident. The cause of chordal rupture in these cases was in part progressive left ventricular dilatation, direct trauma to the anterior cusp of the mitral valve, and possibly a genetic factor.

Seven cases are described, all men between the ages of 45 and 63 years (average 52). None had a history of rheumatic fever and none had active infection. The typical picture was of acute mitral regurgitation into a small left atrium with severe pulmonary oedema which was often resistant to medical treatment. All patients were treated surgically. Anatomical and histological features of the affected valves are described. Early operation with replacement of the aortic and mitral valves is recommended if the present high mortality (5 out of 7, 70%) is to be reduced.

Angiocardiographic/pathological correlations in congenital mitral anomalies

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The angiocardiographic findings were reviewed in 21 patients with congenital mitral valve disease in whom the exact anatomical diagnosis was known from surgery or necropsy. Patients with corrected transposition and simple atrioventricular canal defects were excluded. Contrast medium had been injected immediately downstream to the mitral valve in each patient.

No precise anatomical diagnosis was made in five patients (24%), all of whom had a cleft anterior leaflet or congenital short chordae. In the remainder, the specific diagnosis could have been made by downstream injection alone in 15 (71%). Upstream injection was performed in 13 of these but would have made the precise diagnosis in only 3 (23%). In one patient both upstream and downstream injections were necessary.

The anomalies giving rise to characteristic angiocardiographic appearances were parachute valve, atresia, annular hypoplasia, dysplasia, anomalous arcade, and anomalies associated with subaortic stenosis.

Thus injection downstream to the valve is more valuable than upstream injection, because information can be obtained not only about tensor apparatus, but also about annular dimensions and the patency and competence of the valve. The ability to show the relation of the mitral annulus to the primitive ventricle had important practical and theoretical consequences in two patients with mitral atresia and primitive ventricle.

Isotope electrocardiograph-gated angiocardiography

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A technique has been devised for assessing cardiac structure and function by studying one cardiac cycle after an injection of ^{99}mTC HSA (0·15 mCi/kg) into an anticubital vein, using a gamma camera and low energy collimeter. Synchronized triggering of the R wave of the electrocardiogram is used in conjunction with a small computer for data storage and processing. The anatomy of the heart is delineated by sequential passage of the bolus of isotope through the various chambers.

Thirty-one patients have been studied: 8 with hypertrophic obstructive cardiomyopathy, 9 with valvular disease, 6 with left-to-right shunts, 4 with ischaemic heart disease and dyskinesia of the left ventricle, and 4 with normal hearts.

The computer has been programmed to generate time-activity curves to obtain volume and flow values by isotope dilution curves. The radiocardiograms thus made have permitted measurement of cardiac output, pulmonary transit time, shunt ratios, ejection fractions, and ventricular volumes.

The radiation dose involved is 1 per cent of that during angiocardiography using contrast medium.

Importance of patient-selection in evaluation of cardiac ambulance service

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This paper describes an evaluation of a cardiac ambulance service manned by trained ambulance personnel.

The overall mortality of patients with heart attacks, including those dead on arrival at hospital and those dying in hospital, was 40 per cent in the group carried by the cardiac ambulance, compared with 51 per cent in the group carried by the routine ambulance service when the cardiac vehicle was not available. However, the apparent reduction in mortality associated with the cardiac ambulance was balanced by a high mortality (68%) among patients brought to hospital by a routine ambulance at times when the cardiac vehicle was available but not used. This high mortality was associated with a short duration of symptoms, a heart attack occurring away from home, and a call for an ambulance by a member of the public rather than a general practitioner.

It is suggested that there was inadvertent selection of low risk cases for transport by the cardiac ambulance, and the difficulties of assessing the value of such services will be discussed.

Atrial receptors and a possible naturally occurring diuretic agent

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Atrial receptors are believed to be one link in the regulation of blood volume. These receptors are known to discharge less frequently in heart failure in animals (Greenberg *et al.*, 1973). In normal animals stimulation of atrial receptors produces a diuresis which is thought to be mediated by a diuretic agent (Kappagoda *et al.*, 1975). The present report is concerned with experiments in which a bioassay was used as a possible means of detecting this agent.

Distension of balloons to stimulate atrial receptors in anaesthetized dogs resulted in a diuresis; plasma samples were obtained. Malpighian tubules of *Rhodnius prolixus* (blood sucking bug) were suspended in test and control plasma; the mean difference in secretion of the tubules (test < control) was 27±7·1 per cent (SEM; $P < 0{\cdot}01$). A similar result was obtained after extracting the plasma with butanol. These differences were abolished by cutting or cooling the vagi.

It is concluded that the bioassay using the Malpighian tubules of *Rhodnius prolixus* is capable of detecting a difference between control and test plasma. This difference, like the increase in urine flow, is dependent on the presence of intact vagi. It is suggested that the substance detected by the tubules may be the hypothetical diuretic agent.

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Autonomic features of supraventricular tachycardia

D. H. Dighton
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Forty patients with electrocardiographic evidence of paroxysmal supraventricular tachycardia were investigated, using previously introduced autonomic methods of evaluating atrial pacemaker function (Dighton, 1974). The atrial rate responses to a Valsalva manoeuvre and an intravenous bolus dose of isoprenaline (5 μg/70 kg B.W.) were obtained with patients in sinus rhythm and compared with the responses of 22 normal control subjects.

On the basis of routine electrocardiographic analysis and autonomic responses, three groups emerge.

1) 14 cases: Atrial flutter or fibrillation associated with sinus rhythm; 3 of the 14 cases had reduced autonomic responses, indicating sinoatrial disease, one thyrotoxic had supersensitive responses and the remaining 10 cases were normal to testing.

2) 10 cases: Atrial flutter of fibrillation associated with sinus bradycardia (rate < 55/min at rest). Five of the 10 cases had sinoatrial disease while the remaining 5 were normal on investigation.

3) 16 cases: Rapidly conducted atrial tachycardia of undefined mechanism, associated with normal sinus rhythm at times. No electrocardiographic evidence of pre-excitation. One case had responses indicative of sinoatrial disease; 6 were entirely normal; and 9 had responses greater than any control subject.

Results of this investigation suggest 3 possible mechanisms for supraventricular tachycardia: sinoatrial disease, physiological (or undetectable abnormality), supersensitivity to catecholamines. Those with sinoatrial disease may need to be followed with a view to pacing since digoxin and cardiac suppressants may be contraindicated. Those with normal atrial pacemaker function should be able to take these drugs without complication. In those with supersensitivity to catecholamines causes for anxiety and aggravation should be sought and thyrotoxicosis carefully excluded, or treated as necessary. Anxiolytic drugs and beta-blockers may prove the most useful drugs in this group of patients.

Reference

Dighton, D. H. (1974). Sinus bradycardia. Autonomic influences and clinical assessment. *British Heart Journal*, **36**, 791.

JOINT SYMPOSIUM WITH THE CARDIAC MUSCLE RESEARCH GROUP

Clinical prospects for reducing infarct size

D. A. Chamberlain
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The prognosis after acute myocardial infarction depends to an important degree upon the extent of muscle necrosis. Ultimate infarct size is determined in part by events that occur some hours after the onset of symptoms. The balance between delivery and use of oxygen within an ischaemic area influences the degree of hypoxia and the secondary pathological changes which lead to irreversible cell death. Therapy should, therefore, be directed to reducing myocardial oxygen requirement and preserving the integrity of cells within the damaged myocardium. Experimental evidence suggests that infarct size can be limited in this way, and numerous varieties of treatment have been proposed for clinical use. None has yet gained wide acceptance partly because of the difficulty in assessing their value. The prospect of translating promising experimental techniques into routine clinical procedures awaits the development of practical methods for monitoring the extent of myocardial injury and necrosis.

What is the evidence that therapeutic intervention in acute myocardial ischaemia can preserve useful functioning myocardium?

M. Thomas
King Edward VII Hospital, Midhurst, Sussex

Therapeutic intervention in the natural history of disease can be dramatically obvious in its effect, but more often new treatment requires detailed analysis before acceptance or rejection as 'orthodox'. Proof of efficacy varies widely in quality, from direct knowledge of lives saved, improvement in tissue function, or symptomatic aid in man, to indirect suggestion from experimental data and theory. In myocardial ischaemia, benefit may be had from a primary increase in blood supply, a reduction in metabolic demand, or factors that attenuate intracellular metabolic disease at a given level of ischaemia. Metabolic approaches, purporting to ameliorate intracellular disease and preserve the myocardium for future function are difficult to assess. Prevention of catecholamine drive, modifying potassium and glucose metabolism, blocking free fatty acid utilization are subject to controversial debate. A particular instance is the use of β-blocking agents in unstable angina and acute myocardial infarction in man. Measurement of their influence in patients is limited and extrapolation from indirect indices of benefit uncertain. We need to examine the proof available and to apportion weight to the case for changing clinical practice.

Does ST segment mapping accurately reflect myocardial damage?

J. H. Wittig
Department of Pharmacology, Oxford University

Over the past several years there has been increasing interest in the development of tools which might give the clinician the ability to quantify the ontology of myocardial ischaemia in patients experiencing acute myocardial infarction.

Such tools, by necessity, would need to predict the future history of electrical and mechanical function of acutely ischaemic areas. If it were possible to predict the hysteresis of an infarcted area, then one could make evaluations of various interventions which might change the predicted history of an area of ischaemic myocardium.

Naturally the quantification of unipolar or bipolar electrocardiograms, whether epicardial, transmyocardial, or chest wall would seem a reasonable way to evaluate ischaemia.

In the early 1960's Sayen and colleagues showed that unipolar epicardial electrogram ST segments were poor indicators of transmyocardial ischaemia when compared with intramyocardial oxygen electrodes and myocardial dyskinesis, especially in larger infarctions in dogs.

This technique was revived in the early 1970's by Maroko and Braunwald who suggested that epicardial unipolar ST segment elevations reflected myocardial cellular injury, and that the magnitude of ST segment elevation correlated well with altered myocardial metabolism and subsequent histological evidence of myocardial infarction. This group and several others have subsequently extrapolated these techniques in clinical praecordial ST segment mapping of anterior myocardial infarctions.

Recently, however, several studies have shown poor correlation of the unipolar epicardial ST segment mapping techniques with the microcirculatory perturbations of acute ischaemia in dogs. These studies have again questioned the reliability of unipolar ST mapping.

We would like to clarify these conflicting data by examining the biophysics of unipolar ST elevation.

Serum enzymes: what can they really tell us about myocardial damage?

D. J. Hearse
Royal Postgraduate Medical School, London W12 0HS

Associated with acute myocardial ischaemia are numerous metabolic and morphological changes. The time of onset and magnitude of these tissue changes are dependent upon the duration and severity of ischaemia. Of the many hundreds of biochemical changes that occur in the myocardium, a few, for example potassium loss, pyruvate and lactate changes, and the leakage of intracellular cardiac enzymes to the plasma, have been singled out as valuable markers of ischaemic damage. The observed leakage of cardiac enzymes has formed the basis of modern diagnostic enzymology. The state of the art has evolved such that the appearance of one or two cardiac enzymes in the plasma is not only used for the diagnosis of the presence, approximate magnitude, and time of onset of myocardial infarction but it has been suggested that mathematical analysis of enzyme leakage allows us to predict the progression and exact size of the infarct. What is the basis of these suggestions? Why and by what mechanism do enzymes leak from the cell? What are the cellular implications of enzyme leakage and does it signal the onset of irreversible damage? Why do we choose CK, LDH or AST? Are they in some way unique? Can we really equate enzyme leakage with cell death? Is there a precise and defined relation between the rate and extent of enzyme release and the amount of cell damage? How specific are these tests and what benefits are there in studying isoenzyme as opposed to enzyme leakage?

YOUNG RESEARCH WORKERS' PRIZE

Learned voluntary control of autonomic functions: investigations of mechanisms and possible clinical applications

T. Pickering
Radcliffe Infirmary, Oxford

The autonomic nervous system is not usually thought to be susceptible to direct voluntary control, and autonomic changes during voluntary acts are assumed to depend on changes produced by skeletal muscles. The ability to learn more direct voluntary autonomic control was investigated with biofeedback techniques in patients in whom skeletal muscle control was severely impaired.

In 8 patients with poliomyelitis or muscular dystrophy small (±3 mmHg (0·4 kPa)) but significant changes of diastolic pressure could be produced in either direction during 90-second trials, without changes in breathing or muscle tension.

Twenty-five per cent of tetraplegic patients with complete cervical cord transections learned to increase systolic pressure (+7 to +24 mmHg (+0·9 to +3·2 kPa) during 5-minute trials. Heart rate also increased, but decreased during spontaneous pressure rises. Voluntary pressure control could be blocked by atropine (which itself raised pressure), suggesting a vagal mechanism. Respiratory manoeuvres and attempted muscle contraction could not reproduce the voluntary pressure rises.

It is concluded that voluntary control of autonomic functions may be learned, and is not necessarily secondary to changes in skeletal muscle. Possible therapeutic applications are described.

Glycoside inotropy and K^+ efflux in presence of an acidosis

Philip A. Poole-Wilson
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Although the cardiac glycosides are widely used in clinical practice, their mode of action is controversial. The augmentation of Ca^{++} influx associated with their inotropic effect has been attributed to an increase of intracellular sodium or to an increase of K^+ efflux. This study was designed to examine these two hypotheses.

The inotropic effect of $1 \cdot 25 \times 10^{-6}$M acetylstrophanthidin (ACS) and the influx and efflux of $^{42}K^+$ were studied in the arterially perfused rabbit interventricular septum under control conditions and during a respiratory acidosis. An increase of the CO_2, with which the modified Ringer's solution was equilibrated, from 5 to 30 per cent reduced the perfusate *p*H from 7·37 to 6·66. The increment of developed tension in the presence of ACS was $3 \cdot 0 \pm 0 \cdot 2$ g ($n = 10$) under control conditions but was greater, $7 \cdot 1 \pm 0 \cdot 9$ g ($n = 9$) in an acidosis ($P < 0 \cdot 001$). The net K^+ loss resulting from an increase of K^+ efflux was $1 \cdot 8 \pm 0 \cdot 2$ mmol/kg wet wt in control experiments but only $0 \cdot 1 \pm 0 \cdot 1$ mmol/kg wet wt under acidotic conditions ($P < 0 \cdot 001$); in 7 out of 9 experiments in a respiratory acidosis no increase of K^+ efflux occurred despite a striking positive inotropy. In three septa K^+ influx was reduced by ACS during a respiratory acidosis.

These results indicate that though ACS in an acidosis inhibits Na^+–K^+ ATPase and causes an inotropic effect, it does not increase K^+ efflux. K^+ efflux cannot be coupled with Ca^{++} influx or be closely linked to the mechanism of the inotropy induced by glycosides. The results give further support to the proposal that the inotropic effect of glycosides is secondary to enchancement of a Na^+–Cr^+ exchange system. The findings are of relevance to the use of glycosides in those clinical situations in which there exists an intracellular acidosis.

Pituitary-adrenal axis during cardiopulmonary bypass

K. M. Taylor
Royal Infirmary, Glasgow

The response patterns of plasma cortisol, corticotrophin (ACTH), and growth hormone were investigated in patients undergoing elective cardiac surgical procedures using normothermic cardiopulmonary bypass. Patients undergoing closed mitral valvotomy were used as controls.

Total plasma cortisol levels fell at the onset of extracorporeal circulation (ECC) and did not rise significantly throughout the period of ECC. The peak cortisol level was delayed, occurring at 24 hours postoperatively. This pattern was highly significantly different from the control patients ($P < 0 \cdot 001$) who showed the typical cortisol stress response pattern.

Stimulation of the adrenal cortex during ECC with synthetic ACTH produced a positive response (i.e. a rise in plasma cortisol >200 nmol/l) in all patients studied. This group was significantly different from 6 mitral valvotomy patients who had no response to synthetic ACTH administered during operation ($P < 0 \cdot 01$).

Plasma ACTH levels showed a progressive fall during the period of ECC from a pre-ECC primary peak such that levels in the latter half of ECC were in the non-stress range (i.e. <100 ng/l). One hour after the end of ECC a striking secondary ACTH response was seen. Plasma growth hormone levels showed a similar response pattern to that of ACTH.

It is concluded that the cortisol response during cardiopulmonary bypass differs significantly from the typical cortisol response to stress, and that the differences appear to be related to the period of extracorporeal circulation. The secretion of cortisol during ECC is submaximal but the adrenal will still respond to exogenous ACTH. In addition, the response patterns of ACTH and growth hormone suggest that the reduced cortisol secretion is a direct result of generalized anterior pituitary hypofunction during bypass.

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British Heart Journal, 1976, **38**, 322.

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(4) Submit a curriculum vitae written in Spanish.

(5) Present the research work in the language of the country where the work was done, together with a copy translated into Spanish, which must include the same text and photographic information contained in the original.

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The texts of research and the curriculum vitae must be received by the Patronato Miguel Servet, 'Fundación General Mediterránea', Velézquez-12, Madrid-1, Spain, before 1 May 1976.

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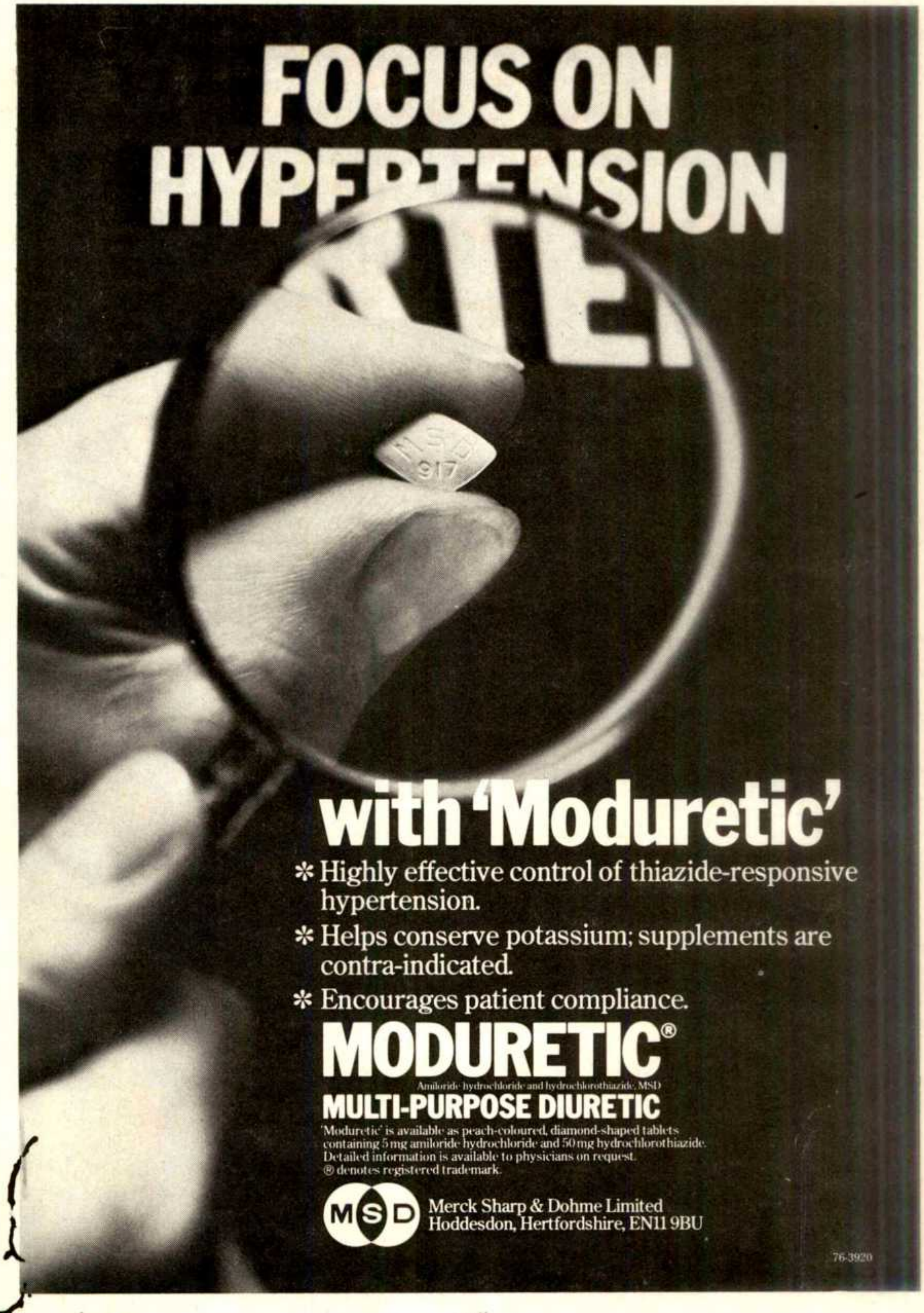

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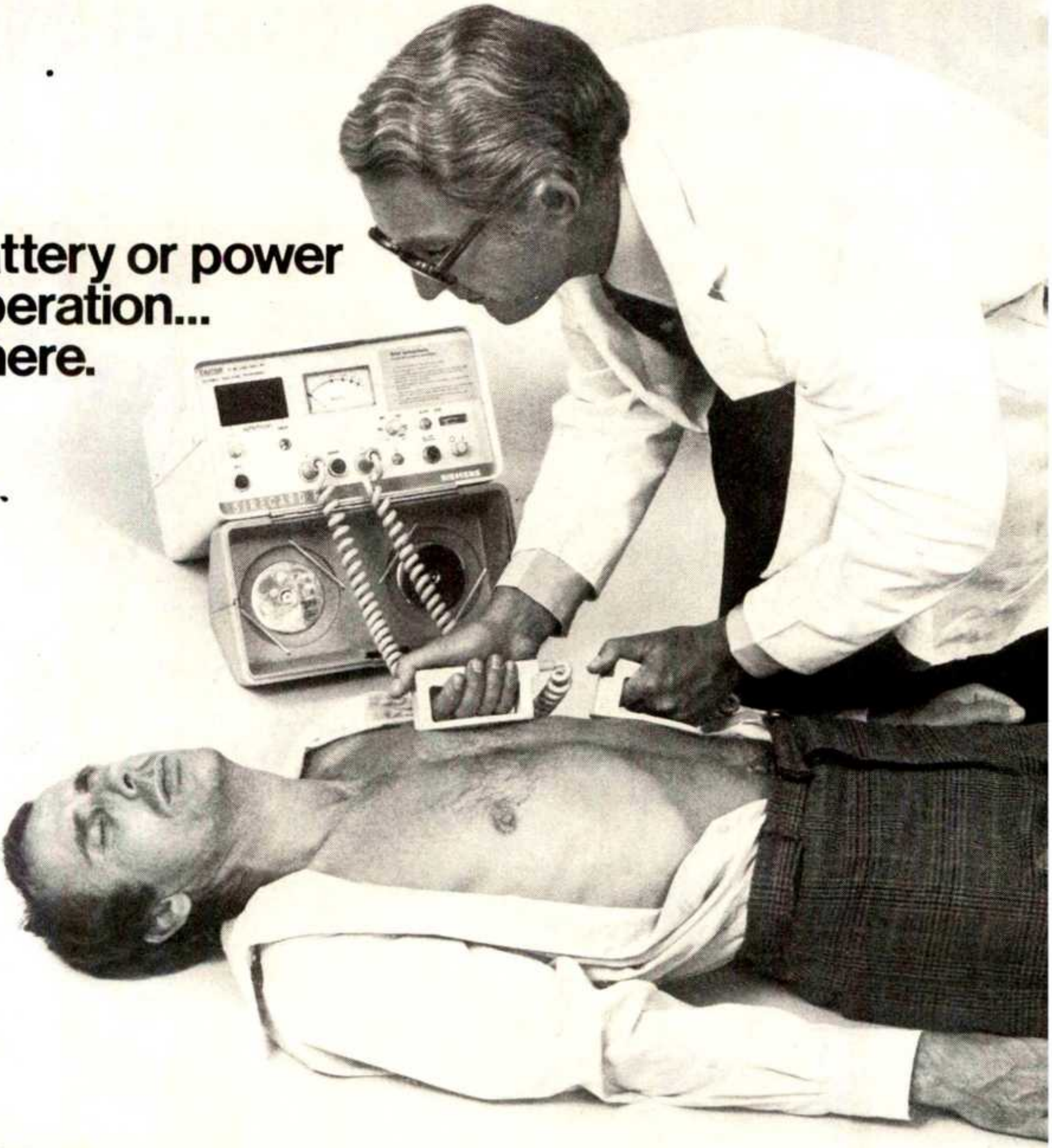

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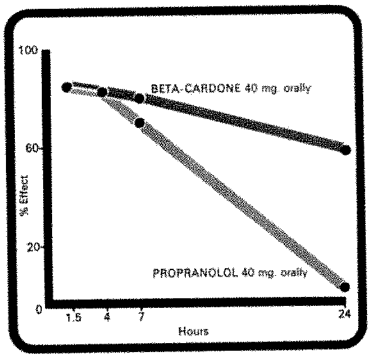

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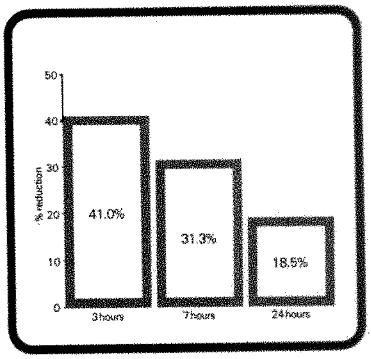
Eur. J. Pharmac. (1969), 8, 79.



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Eur. J. clin. Pharmac. (1976) in press

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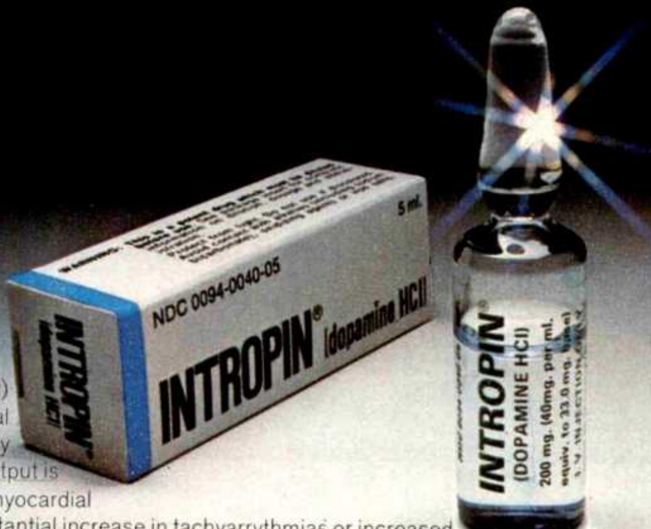

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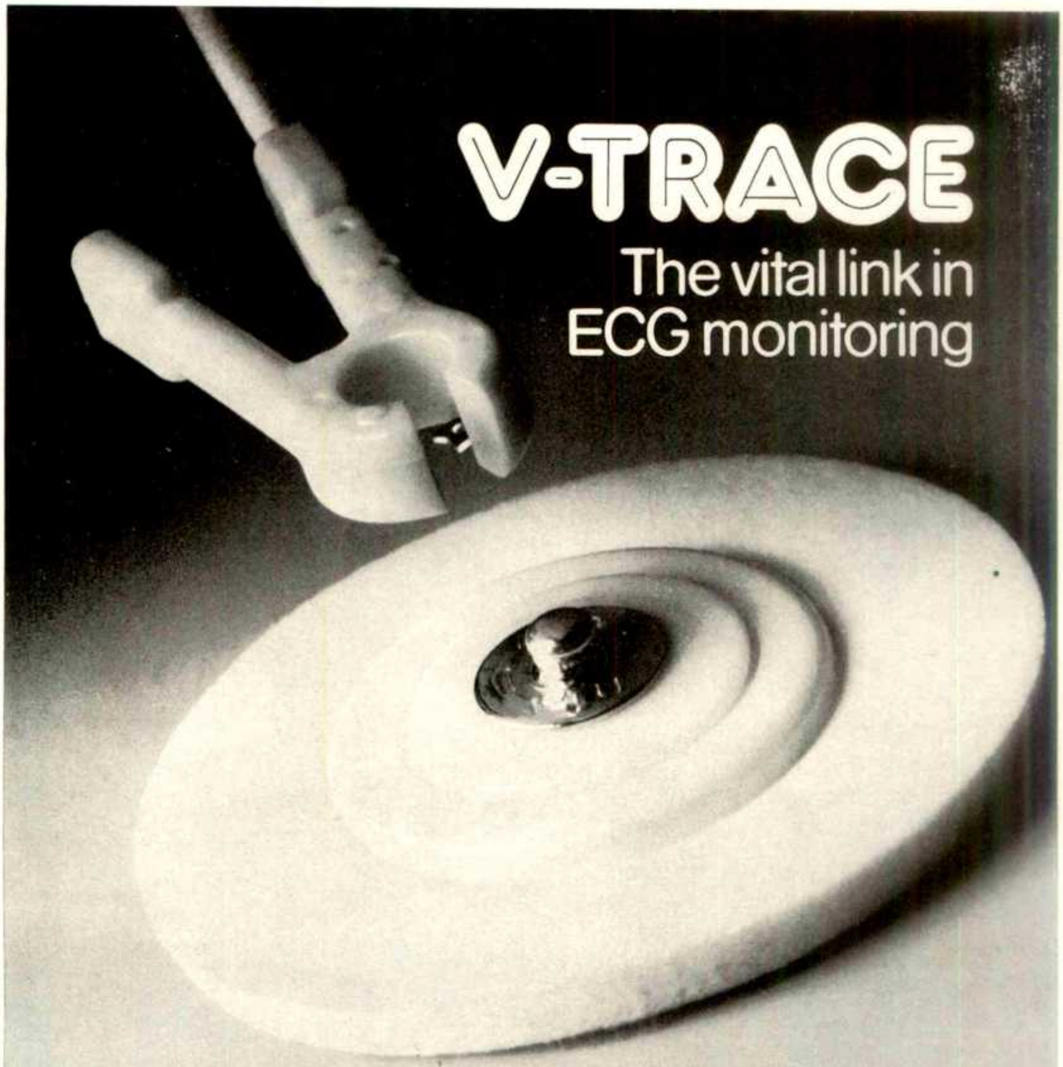

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In acute stress[1]

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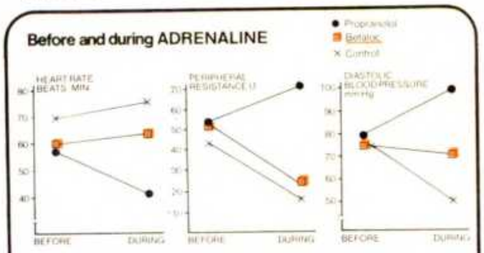

Normally, heart rate and blood pressure responses to exercise are inhibited equally by Betaloc and propranolol. During adrenaline infusion (simulating stress) responses differ markedly.

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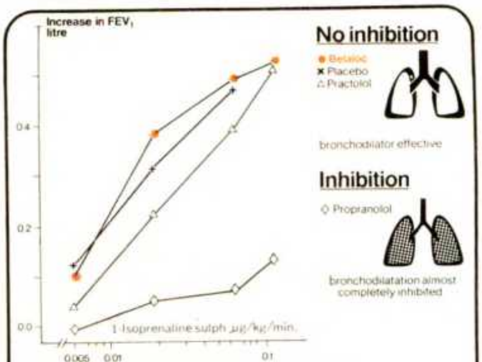

Asthmatic patients: showing no inhibition of isoprenaline effect by Betaloc, compared with almost complete inhibition by non-selective propranolol.

[1] (1975), *Acta pharmacol et toxicol.*, 36, Suppl. V, 39-68 University of Gothenburg, Sweden.

[2] Clinical Report (1975), University of Gothenburg, Sweden.

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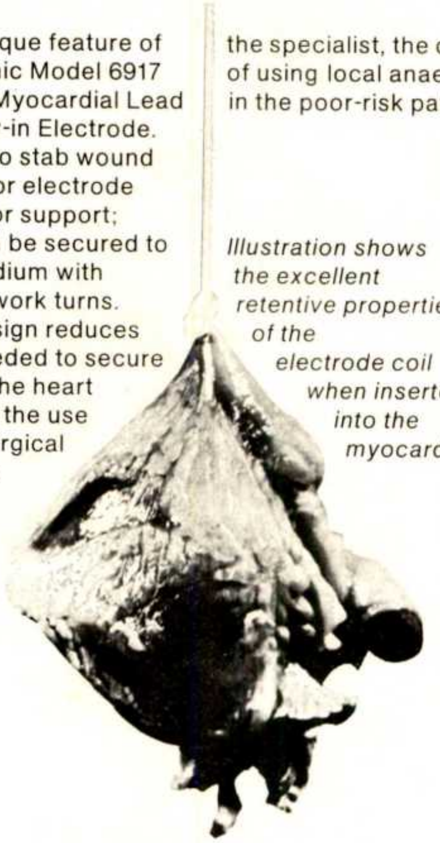

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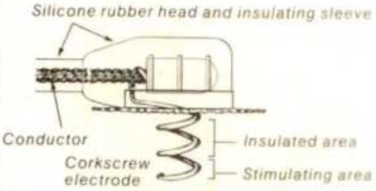

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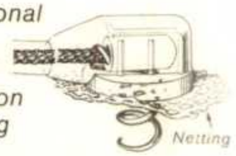

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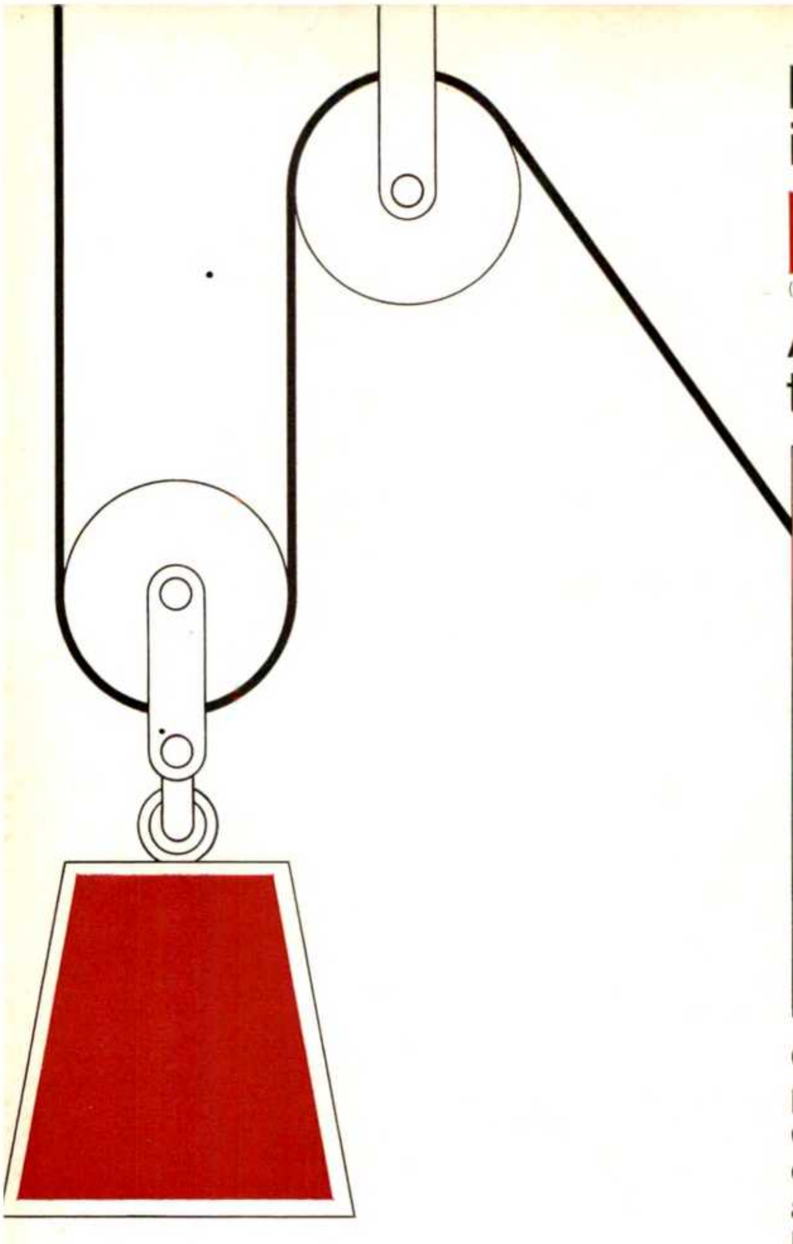

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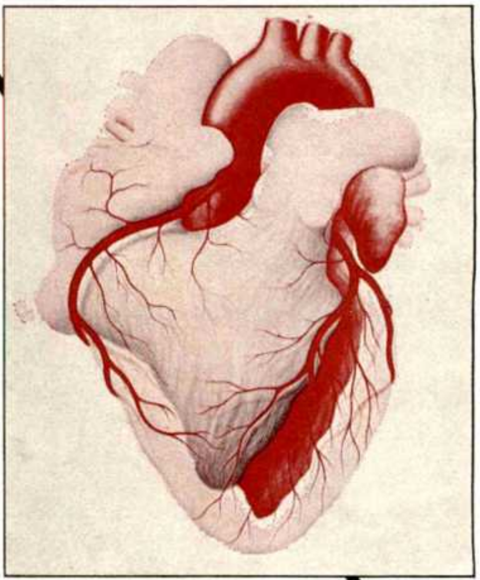

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British Heart Journal, 1976, 38, 323–326.

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Fergus J. Macartney, Elliot A. Shinebourne, and Robert H. Anderson[1]
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It is impossible to discuss complex cardiac anomalies without clearly differentiating between relations and connexions. Relations describe broad spatial interrelationships of two cardiac structures. In contrast, connexions specifically state the fashion in which two structures are connected one to the other irrespective of their relations. Connexions and relations may be, and indeed usually are, the same. Unfortunately this is not always the case, which is precisely why we prefer the concept of connexions. To take two examples; firstly, it is possible for the normally situated right atrium to be normally connected to the morphological right ventricle, but for this right ventricle to be left sided (Anderson, Shinebourne, and Gerlis, 1974). Thus the connexions are normal, but the relations of the ventricles are clearly abnormal, since they are spatially inverted. Secondly, it is usual for the aorta to be posterior and right sided with relation to the pulmonary artery in a patient with situs solitus and normally connected ventricles. However, it has been shown that the normally related aorta in this situation can take origin from the *right* ventricle and not the left (Van Praagh *et al.*, 1971; Wilkinson *et al.*, 1975). Using a relations concept, it is not possible to describe this connexion as transposition. However, unequivocally the ventriculo-arterial connexion is one of transposition (Van Praagh *et al.*, 1971; Wilkinson *et al.*, 1975). It is the intracardiac connexions which are determined by embryogenesis. These in turn determine the haemodynamic condition of the patient and the corrective surgery which may be required. In contrast, relations may be affected by multiple extracardiac events, and by rotation of the heart following completion of its normal development. Thus, we believe that a nomenclature based upon connexions is both more meaningful and more helpful than one based upon relations. This holds good not only for the embryologist, but for the cardiologist, surgeon, radiologist, and pathologist.

In this issue of the *British Heart Journal*, de la Cruz and her colleagues (1976) propose a nomenclature together with rules for diagnosis which are based entirely upon relationships. If these rules are applied to the two cases quoted above, then diagnoses of, firstly, a discordant atrioventricular relation and, secondly, of normally related great arteries without transposition would be made. Such diagnoses are not only misleading, but could be positively dangerous in a clinical context.

It is also suggested that viscero-atrial situs should be established from hepatic and inferior vena caval position, and ventricular position from examination of the relationships of the infundibula and great arteries. In order to establish the latter relationships, de la Cruz *et al.* (1976) provide complex and lengthy 'rules'. This seems to us to be using a sledgehammer to crack a nut.

Angiocardiographically, ventricles need only be defined in terms of their intrinsic qualities. With the possible exception of coronary arteries, it is actually misleading to refer to other structures. One of us (F.J.M.) has worked in a centre in which, for the past five years, all symptomatic complex 'transpositions' and 'malpositions' of appropriate age have been referred for corrective surgery. Ventricular localization has been carried out solely by examination of the diastolic shape and trabecular pattern after injection of contrast medium into both ventricles, and atrioventricular connexion established by inspection of the atria, catheter course, and atrioventricular valves. No error in these respects has been made in over 1300 cases studied. This experience is not regarded as anything special, but as normal for any catheterization laboratory involved in the preoperative assessment of such patients. 'Rules' for predicting ventricular positions are by no means a new proposition. Twelve years ago, an attempt was made at prediction of ventricular position from great arterial position using the 'loop' rule (Van Praagh *et al.*, 1964). This 'rule' was subsequently shown to be inaccurate in about 30 per cent of cases (Carr *et al.*, 1968). To his credit, Van Praagh subsequently admitted its fallibility (Van Praagh, 1972). By contrast, when the 'rules' put forward by de la Cruz and Nadal-Ginard (1972) were shown to have exceptions, a new term (arterio-ventricular discordance) was coined to describe those hearts which broke the rules (de la Cruz *et al.*, 1974). If the 'rules' themselves are confusing, this term is endowed with even more potential to confuse. The term 'discordance' is used with an entirely different meaning from its application to atrioventricular relations (or connexions). In the latter situation, discordance indicates a situation opposite to normal. By analogy, a discordant arterio-ventricular relation (or connexion) should also be the opposite of normal, namely transposition. This is indeed the definition of ventriculo-arterial discordance given by Kirklin and his colleagues (1973). But, according to de la Cruz *et al.* (1974, 1976) arterio-ventricular concordances and discordances can each coexist with either transpositions or crossed (normally related) great arteries.

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There are additional fundamental scientific objections to the classifications proposed by de la Cruz and her colleagues (de la Cruz and da Rocha, 1956; de la Cruz and Nadal-Ginard, 1972; de la Cruz *et al.*, 1974, 1976). De la Cruz and Nadal-Ginard (1972) laid down other 'rules' for establishing atrial situs. They defined, as others had done (Van Praagh *et al.*, 1964), situs solitus, situs inversus, and heterotaxias. They then stated that, 'Heterotaxias . . . due to their anatomic and embryologic features . . . do not conform to the rules which apply to situs solitus and inversus' (de la Cruz and Nadal-Ginard, 1972). However, they do not indicate how heterotaxias are to be clearly differentiated in life from situs solitus and inversus. We would point out a mid-line liver is a very poor indicant of situs ambiguus (heterotaxia). From the detailed reports of 84 patients with abnormal cardiac situs or position from the Hektoen Research Institute, it is clear that a mid-line liver is the exception rather than the rule in asplenia and polysplenia (Lev *et al.*, 1968, 1971; Liberthson *et al.*, 1973). Had atrial situs been predicted from liver position, it would have been correct in only 37 per cent of cases. In contrast, lung lobulation would have given the correct prediction in 72 per cent of cases. Bronchial visualization, an easily performed clinical investigative technique, could well have given even better prediction. A more recent study has shown that measurement of bronchial lengths enables clear distinctions to be made between thoracic lateralization (solitus or inversus) and thoracic isomerism (heterotaxy) (Partridge *et al.*, 1975).

Similar divergences in interpretation and opinion are found with regard to 'arterio-ventricular' relations, or, as we would prefer to describe them, ventriculo-arterial connexions. De la Cruz and her colleagues (1956, 1972, 1974, 1976) describe normal relations, transposition and an intermediate group named 'partial distorsions' (Angelini and Leachman, 1973). These terms describe *only* relations, so a double outlet ventricle connexion can, according to de la Cruz *et al.* (1976), coexist with any of these relations. We submit that this concept is equally confusing. It has been convincingly shown in recent years, both from angiographic studies (Guerin *et al.*, 1970) and from study of necropsied material (Lev *et al.*, 1971; Goor and Edwards, 1973; Anderson *et al.*, 1974a) that a spectrum of abnormalities exists between transposition on the one hand and double outlet ventricle on the other. When a spectrum exists, it is not possible to make clear-cut distinctions. Instead, an arbitrary distinction is necessary such as that proposed by Kirklin *et al.* (1973) demanding more than one and a half great arteries arising from the same ventricle for the definition of a double outlet ventricle. Van Praagh (1973) has martialled excellently the arguments against the description 'partial distorsion'. We would add that unless specific 'rules' are laid down for the distinction between partial distorsions and other trunco-conal morphologies, the 'rules' for arterio-ventricular discordance are valueless, since partial distorsions are specifically excluded from these 'rules' (de la Cruz *et al.*, 1976). This point is particularly relevant in the case of anatomically corrected malposition. In order to explain why this does not obey the rules, de la Cruz *et al.* (1974), 1976) state that this is a partial distorsion. If the case descriptions to which they refer (Van Praagh and Van Praagh, 1967; Anderson Arnold, and Jones, 1972) are consulted, it is found that in three of four cases the aorta was specificially stated to arise anteriorly to the pulmonary artery. According to de la Cruz's own nomenclature (1974, 1976), this fact would make them 'transpositions' rather than 'partial distorsions'. Partial distorsion should surely serve a more useful function than constituting a convenient hiding place for cases which 'break the rules'.

De la Cruz and her colleagues (1976) argue that their hypothesis is based upon embryological facts. It is very difficult to determine what constitutes an embryological 'fact'. We would contend that they refer to 'embryological interpretations'. They discuss their concepts and support them by reference to work of other noted embryologists. When considering contrary views, however, they argue only against the 'conal growth' hypothesis of Van Praagh. If the original argumentation of Van Praagh is read relative to this hypothesis (Paul, Van Praagh, and Van Praagh, 1968), it becomes very evident that the hypothesis was propounded precisely because the classical 'straight septum' hypothesis, which de la Cruz *et al.* (1976) still support, could not account for the anatomy of specimens with transposed arteries. Somewhat ingenuously, de la Cruz *et al.* (1976) fail to mention this point. They also fail to point out that at that time Paul *et al.* (1968) considered a conal *absorption* hypothesis. They did not advance such an hypothesis because they considered it was not supported at that time by embryological investigations, though pointing out that Butler (1952) had shown conal absorption in the chick heart. Paul *et al.* (1968) proposed conal growth because it was supported by *anatomical* fact. De la Cruz *et al.* (1976) suggest that the mechanism of transference of the aorta to the left ventricle is unknown. This is also somewhat ingenuous. The mechanics of this process were elucidated by Pernkopf and Wirtinger (1933) and endorsed by Asami (1969). They were again endorsed by Goor, Dische, and Lillehei (1972). It is surprising that de la Cruz *et al.* (1976) quote the article of Goor as ammunition against Van Praagh *et al.* (1964), but do not comment on Goor's suggestion that transposition results from differential conal absorption coupled with lack of conal inversion. This concept has subsequently received support from the work of Anderson *et al.* (1974b). Above all, de la Cruz *et al.* (1976) do not quote the important paper of Los (1968). His reconstructions in the human convincingly showed that, though the conotruncal ridges formed in spiral fashion, they *fused* in straight fashion. This finding has been confirmed in the chick heart by the investigation of Dor and Corone (1973). Thus in the *normal* heart the conus septum is a straight and not a spiral structure. This, combined with the arguments of Paul *et al.* (1968), plus the embryological studies of Pexieder (1975), convince us that a differential conal *absorption* hypothesis gives a much better explanation of transposition than the 'straight septum' hypothesis promoted so strongly by de la Cruz *et al.* (1976). However, we do not claim these points as facts; they are interpretations. As such they could be wrong. We would request that de la Cruz and her colleagues (1976) review ALL the evidence against their own hypothesis, rather than attacking a conal growth concept which is no longer propounded by its originator (Van Praagh, 1973).

Beyond doubt, de la Cruz and her colleagues have, over the years, made a major contribution to our knowledge of congenital heart disease, particularly in their meticulous descriptions of malformed hearts. In drawing attention to the more controversial aspects of their work, we wish only to stimulate readers to make their own critical judgement on these issues. There is little point in enumerating the inconsistences of a particular viewpoint without providing a convincing and more consistent alternative. It is our hope that a nomenclature based upon connexions rather than relations, as proposed elsewhere in this issue (Shinebourne, Macartney, and Anderson, 1976), will do precisely this.

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Invited article

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Sequential chamber localization—*logical approach to diagnosis in congenital heart disease*

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A nomenclature is described for congenital heart disease employing sequential chamber localization. It is an eclectic system based in part upon the previous classifications of Van Praagh and Kirklin. It links together the atrial, ventricular, and arterial segments of the heart and then permits tabulation of associated anomalies. The atrial segment of the heart can exist as situs solitus, situs inversus, or situs ambiguus. Atrioventricular connexions can be concordant or discordant. In certain circumstances the terms concordant and discordant cannot be used. These are in the presence of primitive ventricle and in the presence of situs ambiguus. Alternative terms are described for these contingencies. Ventriculo-arterial connexions can be (a) normal; (b) transposition; (c) double outlet ventricle; or (d) single arterial trunk. These are defined as connexions; relations are relegated to secondary position. Associated anomalies are categorized in terms of venous return, atria, atrioventricular junction, ventricles, and great arteries. Controversial topics are discussed with regard to previous definitions.

For a nomenclature to be of value in modern paediatric cardiology, it must be capable of describing any combination of cardiac malformations which may be encountered. Furthermore, it should, as far as is possible, allow for the precise classification of such malformations to be made during a patient's life. At the present time, it is usual to define given cardiac malformations as discrete entities, as exemplified by the terminologies agreed upon by the International Society of Cardiology (1970) and the New York Heart Association (1973). However, complex cardiac malformations are being reported with increasing frequency which do not lend themselves to categorization within these rigid classifications. It is our belief that in order to describe such hearts adequately it is necessary to adopt a concept of nomenclature based upon sequential chamber localization. Such an approach has been formulated by Van Praagh and his colleagues (Van Praagh, Ongley, and Swan, 1964a; Van Praagh *et al.*, 1964b; Van Praagh and Van Praagh, 1966; Van Praagh, 1968; Van Praagh *et al.*, 1971; Van Praagh, 1972, 1973). During the evolution of these concepts, Van Praagh has found it necessary to effect radical alterations in certain definitions. In the case of 'transposition', the new definition of Van Praagh *et al.* (1971) provoked considerable controversy (Van Mierop, 1971). However, the new definition was essential since the segmental approach is concerned with descriptions of *connexions*. Because the *same* connexions can exist with considerable variation in spatial *relationships* it has become necessary to relegate relations to a secondary role. This philosophy is exemplified by Kirklin's modification of the segmental approach (Kirklin *et al.*, 1973). We are convinced that this emphasis on connexions is fully justified, and that it aids the understanding of many complex anomalies (Anderson, Shinebourne, and Gerlis, 1974a). This review, therefore, will outline our eclectic nomenclature based upon identification of segmental connexions.

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A: Basis of segmental nomenclature

As the term sequential chamber localization implies, the system is based upon identification of the positions of the different segments of the heart (Table 1), and the nomenclature to be described enables the segments to be 'linked' together. The individual segments considered for the purposes of connexions are the atrial chambers, the ventricular chambers, and the great arteries together with their supporting coni. A full range of anomalies can then be enumerated within this framework by cataloguing in turn anomalies of venous return, deformations of the atria, abnormalities of the atrioventricular junction, malformations of the ventricles, and anomalies of the great arteries (Table 2).

TABLE 1 *Table indicating possibilities for description of three segments of heart*

Segment	*Possibilities*
Atria	Solitus
	Inversus
	Ambiguus
Ventricles	Concordant
	Discordant
	Primitive ventricle
	'd' or 'l' (with situs ambiguus)
Great arteries	Normally connected
	Transposed
	Double outlet ventricle
	Single arterial trunk

TABLE 2 *Examples of anomalies which may occur in the various portions of the heart**

Region	*Examples of anomalies*
Venous return	Anomalous systemic return
	Anomalous pulmonary return
Atrial chambers	Atrial septal defect
	Cor triatriatum
Atrioventricular junction	Atrioventricular canal
	AV valve atresia
Ventricular chambers	Ventricular septal defect
	Anomalous muscle bundle
Great arteries and cono-truncus	Conal septal defect
	Coarctation
	Persistent ductus arteriosus

*This is not meant to be an exhaustive catalogue but only gives typical examples.

B: Chamber localization

In order to connect the chambers together, it is firstly necessary to consider how the different cardiac chambers can be recognized. In our opinion such differentiation must be based upon morphological characteristics as follows:

(1) Morphological right atrium (Fig. 1a)

In the normal heart this chamber receives the systemic venous return. The superior vena cava, inferior vena cava, and coronary sinus enter the smooth walled sinus venarum, which is separated from the trabeculated right auricle by the prominent crista terminalis. The auricular appendage is typically blunt ending. On its septal surface the right atrium exhibits the limbus of the fossa ovalis. Remnants of the embryonic venous valves, the Eustachian and Thebesian valves, commonly guard the entrances to the inferior caval vein and the coronary sinus.

(2) Morphological left atrium (Fig. 1b)

This chamber in the normal heart receives the pulmonary venous return through four pulmonary veins. These veins enter a smooth walled segment which is not separated from the trabeculated auricle by a crista. On its septal aspect, the left atrium presents the flap valve of the septum primum. A characteristic feature of the left atrium is its 'finger-shaped' auricular appendage.

(3) Morphological right ventricle (Fig. 2a)

In the normal heart this ventricle always possesses an infundibulum and contains the tricuspid valve. Though the cusp pattern of the tricuspid valve is variable, its papillary muscle pattern of a single anterior muscle, multiple posterior muscles, and a conal muscle, is typical. The tricuspid valve is separated from the pulmonary valve by the crista supraventricularis while a prominent trabecula septomarginalis is present on the septal surface. The trabeculations of the right ventricle are coarse.

(4) Morphological left ventricle (Fig. 2b)

This ventricle contains the easily recognizable bicuspid mitral valve with its paired papillary muscles. The mitral valve is in fibrous continuity with the aortic valve, consequently there is no infundibulum. The trabeculations of the left ventricle are fine.

C: Plan for sequential analysis

The order of procedures is first to establish atrial situs, second to ascertain atrioventricular connexions, and third to decide the ventriculo-arterial connexions.

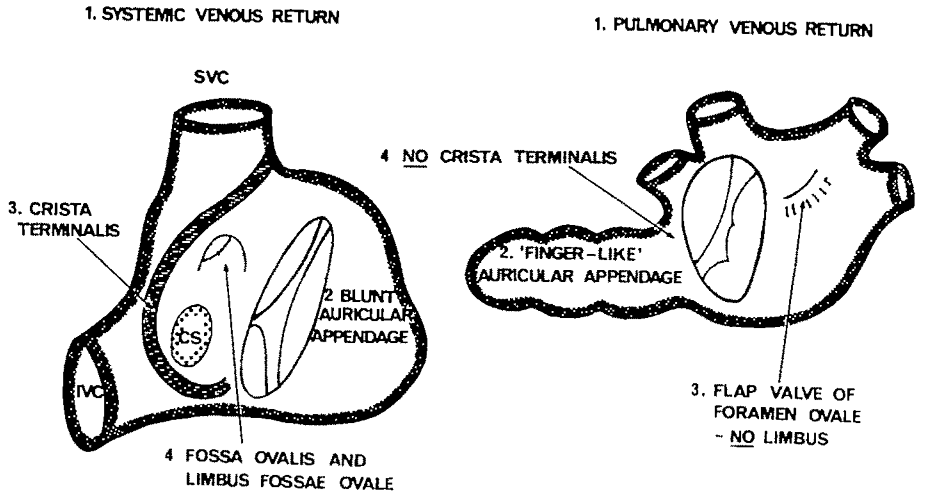

1. SYSTEMIC VENOUS RETURN
SVC
3. CRISTA TERMINALIS
CS
IVC
2 BLUNT AURICULAR APPENDAGE
4 FOSSA OVALIS AND LIMBUS FOSSAE OVALE
1. PULMONARY VENOUS RETURN
4 NO CRISTA TERMINALIS
2. 'FINGER-LIKE' AURICULAR APPENDAGE
3. FLAP VALVE OF FORAMEN OVALE - NO LIMBUS

FIG. 1 *Diagrams illustrating the morphological differences between the normal right atrium (left hand diagram) and left atrium (right hand diagram).*

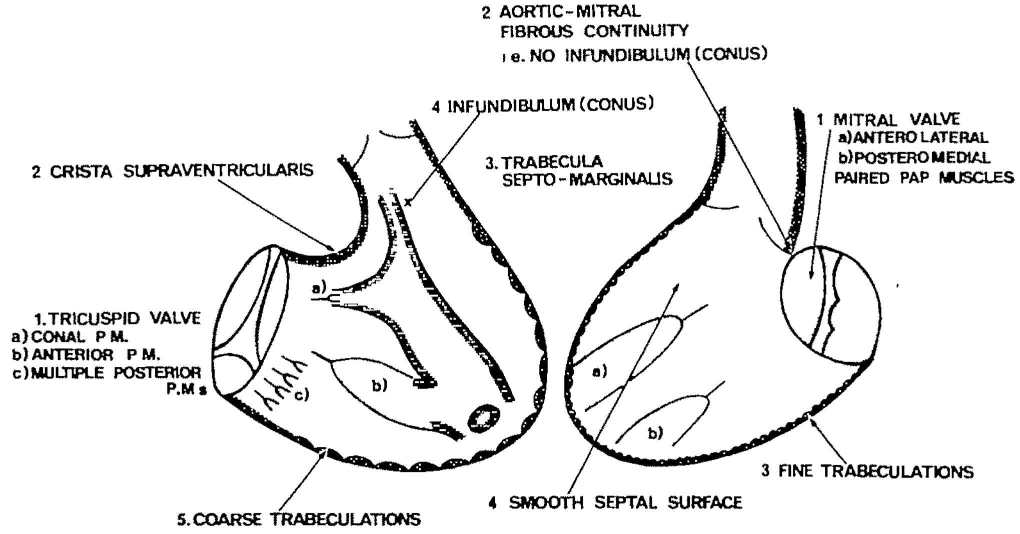
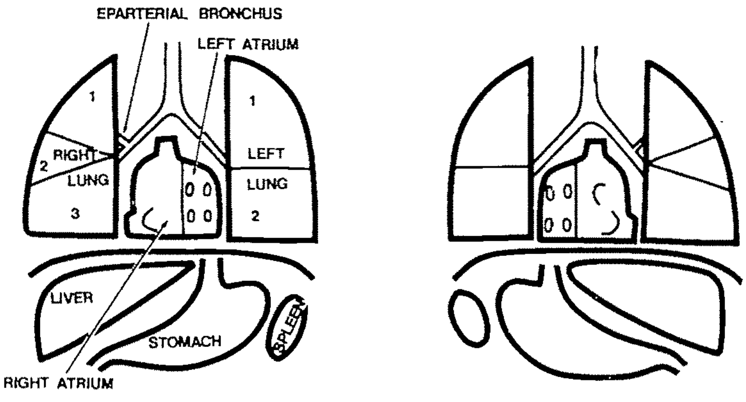


FIG. 2 *Diagrams illustrating the morphological differences between the normal right ventricle (left hand diagram) and right ventricle (right hand diagram).*

(a) Establish atrial situs

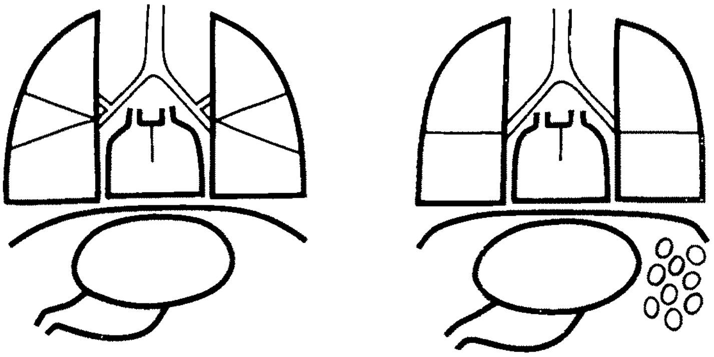
Atrial situs is defined as either *solitus, inversus*, or *ambiguus* (Fig. 3). In situs solitus the morphological right atrium is right-sided and the left atrium is left-sided. In situs inversus the right atrium is left-sided and left atrium right-sided. In situs ambiguus it is not possible to identify separate right *and* left atria on morphological criteria. Thus, a common atrial chamber receiving both systemic and pulmonary venous returns is usually associated with bilateral right or left auricular appendages. The simplest method of establishing these atrial positions



SITUS SOLITUS

SITUS INVERSUS

SITUS AMBIGUUS



BILATERAL RIGHT LUNG

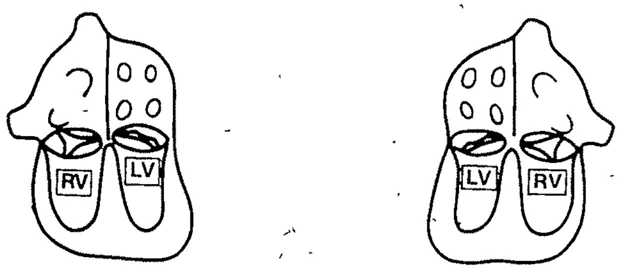
BILATERAL LEFT LUNG

FIG. 3 *Diagram illustrating the features of situs solitus, situs inversus, and situs ambiguus. The latter can exist in two forms: that with bilateral right lung is usually associated with* asplenia *and that with bilateral left lung is usually associated with* polysplenia *(see text for further discussion).*

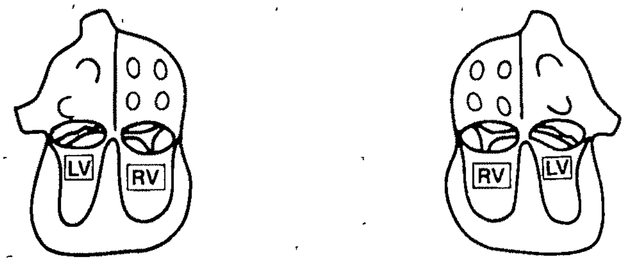
before cardiac catheterization is by examination of the plain and penetrated chest radiograph. Thus, if the liver is right-sided, the inference can usually be made that the inferior vena cava and right atrium are also right-sided and that there is *situs solitus.* Conversely, if the liver is left-sided, then the morphological right atrium will usually be left-sided and viscero-atrial *situs inversus* will be present. When the liver is central, then *situs ambiguus* usually exists. However, in this situation error can be introduced by this method of determining situs from position of abdominal organs. Firstly, situs ambiguus may be 'missed' if there is insufficient gas in the stomach and intestines to outline the liver. Secondly, abdominal and atrial situs do not always correspond (Lev *et al.,* 1968; Hollman, 1968; Hastreiter and Rodriguez-Coronel, 1968; Lev *et al.,* 1971; Losekoot, 1973; Liberthson *et al.,* 1973). It is, therefore, also important to assess thoracic situs, i.e. position of morphological right (trilobed) and left (bilobed) lungs. This can usually be established from examination of the main bronchi on the penetrated chest radiograph (Van Mierop, Eisen, and Schiebler, 1970). In 95 per cent of cases, the radiographic length of the morphological left main bronchus is at least twice that of the right main bronchus, thus making identification of thoracic situs a simple procedure. Where the ratio of bronchial lengths is less than 2, and particularly if it is less than 1·5, then thoracic isomerism (situs ambiguus) is likely to be present. Under these circumstances, or if the bronchi cannot be visualized on the plain film, then bronchial tomography will permit objective assessment of bronchial situs (Partridge *et al.,* 1975). This method allows very sharp lines to be drawn between the three types of situs discussed above. In contrast, the majority of situs ambiguus patients studied by Partridge *et al.* (1975) had lateralized rather than central livers. On the basis of thoracic situs, it is further possible to separate situs ambiguus into two categories of (i) bilateral right lung and (ii) bilateral left lung. These categories have different implications as far as associated cardiovascular anomalies are concerned. It has been previously assumed that bilateral right lungs were always associated with asplenia, whereas bilateral left lungs were always associated with polysplenia. In most studies of necropsy material this has indeed been the case (Moller *et al.,* 1967; P. Stanger, 1975, personal communication). However, the study of Partridge *et al.* (1975) showed that in two patients with haematological evidence of asplenia (presence of Howell-Jolly bodies) the lungs were arranged as for situs solitus and situs inversus, respectively. Furthermore, in the patient with situs solitus, the anticipated severe cardiac anomalies associated with asplenia were not present. In a clinical context, therefore, it appears that the splenic 'state' is considerably harder to establish than thoracic situs, and conveys less information. We are unaware of any exceptions to the rule that atrial situs may be predicted from bronchial anatomy. However, this 'rule' has been tested in relatively few patients. Most data from necropsy studies have been concerned with lung lobulation rather than bronchial anatomy, and lobulation occasionally does not predict atrial situs correctly (Lev *et al.,* 1968, 1971; Liberthson *et al.,* 1973). Equally, lung lobulation does not always correspond with bronchial anatomy (Landing *et al.,* 1971).

(b) Ascertain atrioventricular connexions (Fig. 4)

When the morphological right atrium connects with the morphological right ventricle and the morphological left atrium connects with the morphological left ventricle, then *atrioventricular concordance* is present irrespective of the ventricular positions within the chest (Anderson *et al.,* 1974a). In

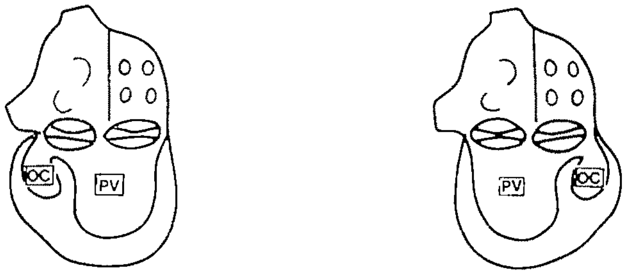


SOLITUS - CONCORDANT INVERSUS - CONCORDANT



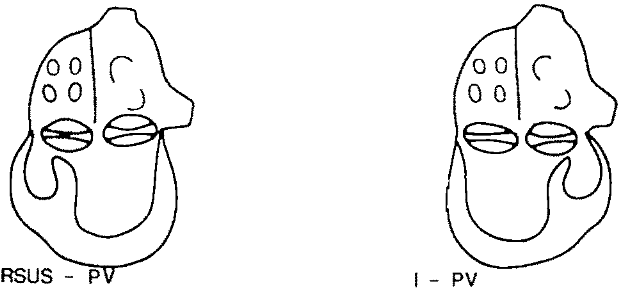
SOLITUS - DISCORDANT INVERSUS - DISCORDANT

FIG. 4 *Diagrams illustrating atrioventricular concordance and discordance. The atria are as depicted in Fig. 3 (RV=right ventricle: LV=left ventricle).*



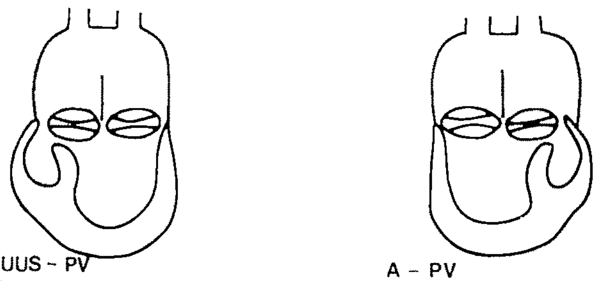
SOLITUS - PRIMITIVE VENTRICLE
OUTLET CHAMBER TO RIGHT

S - PV
OC TO LEFT



INVERSUS - PV
OC TO RIGHT

I - PV
OC TO LEFT



AMBIGUUS - PV
OC TO RIGHT

A - PV
OC TO LEFT

FIG. 5 *Diagram illustrating the position of the outlet chamber (OC) in primitive ventricle (PV) in relation to atrial situs. Since both atrioventricular valves open to the primitive ventricle and cannot be distinguished clinically they are shown as bicuspid structures. The outlet chamber can be to the right or left in association with situs solitus, inversus, or ambiguus (solitus (S), inversus (I), ambiguus (A)).*

contrast, when the morphological right atrium drains to the morphological left ventricle, and left atrium to right ventricle, atrioventricular *discordance* exists, again irrespective of chamber position within the chest. These connexions are established angiocardiographically. The terms concordant and discordant presume the presence of two identifiable atria and two identifiable ventricles. In the living patient, angiographic criteria for the identification of the morphological right ventricle are (a) presence of coarse trabeculations, especially during diastole, and (b) presence of an infundibulum with consequent discontinuity of atrioventricular and semilunar valves. A further feature is the triangular shape of the ventricle in the anteroposterior projection. Criteria for the identification of the morphological left ventricle are (a) a smooth outline to the ventricle during diastole and (b) absence of an infundibulum, the atrioventricular valve being in fibrous continuity with the semilunar valve. In some malformed hearts the morphological left ventricle may possess an infundibulum. The left ventricular chamber usually has a globular appearance in both anteroposterior and lateral projections.

In situations where both atrioventricular valves open into the same ventricular chamber, where one atrioventricular valve straddles a septum, or in the presence of situs ambiguus, use of the terms *concordance* and *discordance* is not justified. When the atrioventricular valves enter a common chamber, or when one valve straddles the septum, having stated visceroatrial situs, we would then indicate that the atria connect with a *primitive ventricle* (Fig. 5, 6). A primitive ventricle exists when the posterior septum normally present between the atrioventricular valves is absent. In our experience, all hearts with primitive ventricles can be further categorized as primitive ventricle with outlet chamber, or primitive ventricle without outlet chamber (Fig. 5, 6; Anderson, Becker, and Wilkinson, 1975b). When an outlet chamber is present, it can be right- or left-sided (Fig. 5). In primitive ventricle it is not possible to distinguish between the tricuspid and mitral valves by angiographic techniques. Indeed, these distinctions frequently cannot be made even by direct examination of necropsy specimens of primitive ventricle. It is, therefore, more accurate to refer to these structures in hearts with primitive ventricle as the right and left atrioventricular valves. Furthermore, in most cases of tricuspid atresia, and in some cases of mitral atresia, the ventricular morphology is identical to that found in primitive ventricle (Anderson and Becker, 1975; Macartney *et al.*, 1976). In these situations, therefore, it would be more accurate to consider the hearts as variants of primitive ventricle and to refer to atresia of the right and left atrioventricular valves respectively. In situs solitus, hearts with straddling right atrioventricular valves have been shown to resemble hearts with primitive ventricle and outlet chamber (Liberthson *et al.*, 1971). Our studies support this viewpoint, and suggest that the septum straddled is the bulboventricular septum between primitive ventricle and outlet chamber rather than the posterior interventricular septum between right and left ventricles (Fig. 7). For this reason, we believe it to be more accurate to refer to these hearts also as primitive ventricle and to avoid use of the terms 'concordant' or 'discordant' in relation to atrioventricular connexions. Examination of our specimens with straddling left atrioventricular valves indicated that in this circumstance also the atrioventricular valve straddled the bulboventricular septum in some cases. More frequently, the straddling left valve was recognizable as a mitral valve and normally formed right and left ventricles were present; in these instances the septum straddled was recognized as the interventricular septum. As Quero Jimenez *et al.* (1973) have indicated, the condition may be termed double inlet right ventricle. Using angiographic criteria, however, the cases could still resemble primitive ventricle with both valves entering a common chamber. Unless we identified two ventricles with certainty, and established the nature of the septum present, we would not use the terms 'concordant' or 'discordant' in this circumstance.

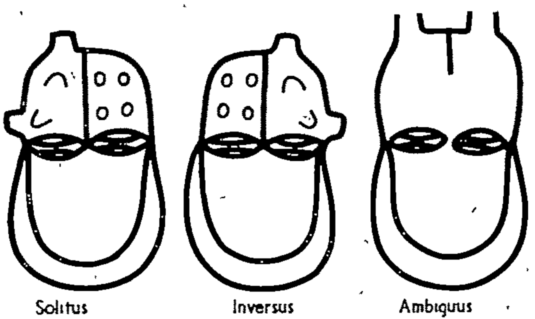


FIG. 6 *Diagram illustrating varieties of primitive ventricle without outlet chamber.*

The other occasion on which the terms 'concordant' and 'discordant' may not be properly used is when there is situs ambiguus (Fig. 8). When situs ambiguus coexists with primitive ventricle, the nomenclature is simply situs ambiguus-primitive ventricle (with or without outlet chamber). When two normally formed ventricles are present, we employ the terms d-loop and l-loop as suggested by Van Praagh *et al.* (1964a).

(c) Decide ventriculo-arterial connexions

As with atrioventricular connexions, this segmental interconnexion is established by angiocardiography carried out in a manner which will profile the anterior interventricular (bulboventricular) septum. There are three basic patterns in which the great arteries may be connected to their underlying ventricles. These are (i) *normal connexions;* (ii) *transpositions;* and (iii) *double outlet ventricle* (Fig. 9). These connexions presuppose identification of two ventricles and a septum (or primitive ventricle and outlet chamber with a bulboventricular septum) and identification of the ventricular origin of both arteries. The situation in which only one great artery can be identified as arising from a ventricle is defined as *single arterial trunk* (Fig. 10). In defining these connexions, no account is taken of either the

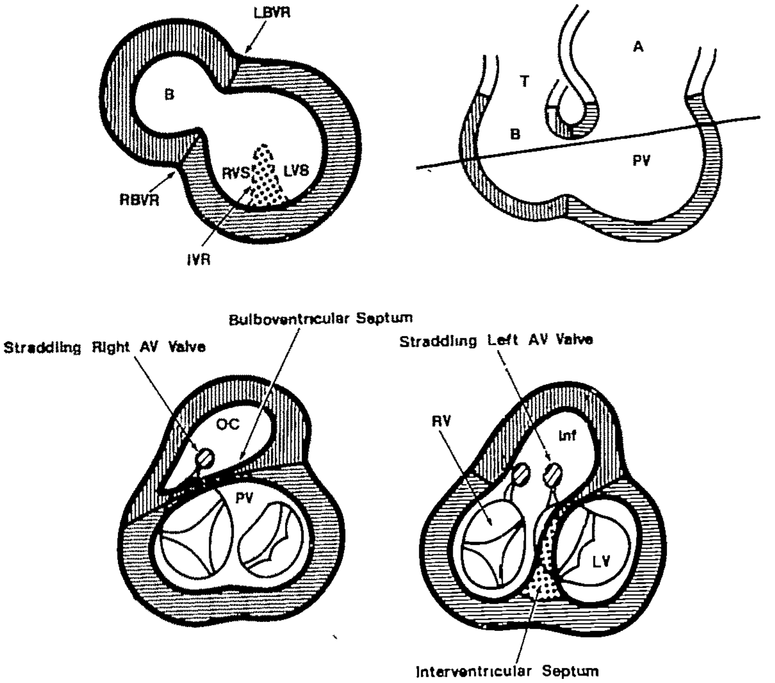
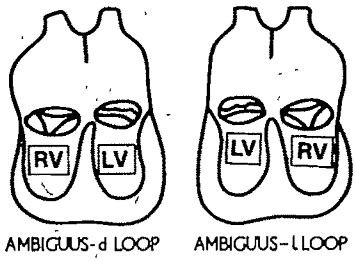


FIG. 7 *Diagrams illustrating the concept of straddling atrioventricular valves. The top right hand diagram is a frontal section through the primitive heart tube (A=primitive atrium; PV=primitive ventricle; B=bulbus; T=truncus). The top left hand diagram is a cross-section at the level of the line. The right and left bulboventricular ridges (LBVR, RBVR) separate bulbus from primitive ventricle. The primitive ventricle itself is divided into the right ventricular sinus (RVS) and left ventricular sinus (LVS) by the interventricular ridge (IVR). Should the bulbus persist as an outlet chamber (OC) with primitive ventricle (PV), then the right atrioventricular valve can straddle the bulboventricular septum (lower left hand diagram). The left atrioventricular valve may also straddle the bulboventricular septum in primitive ventricle with outlet chamber. Further (lower right hand diagram) the mitral valve may also straddle the interventricular septum when right and left ventricles are normally separated. (Inf=infundibulum.)*

spatial interrelations of the arteries or the condition of their coni. These may be subsequently specified if so desired.

(i) Normal connexions The great arteries are normally connected when the aorta arises from the morphological left ventricle (or primitive ventricle) and the pulmonary artery arises from the morphological right ventricle (or outlet chamber). In almost all circumstances such normally connected arteries will also be normally related. The normally *related* aortic valve is posterior and on the opposite side from the morphological left ventricle with respect to the pulmonary valve. Thus, when the left ventricle is left-sided the normally related aortic valve is to the right of the pulmonary valve. In contrast, when the left ventricle is right-sided the normally related aortic valve is left-sided. Rarely will the situation be encountered in which the great arteries are normally connected but in which the valvar interrelations are not normal as described above. This ventriculo-arterial relation has been termed anatomically corrected malposition (Van Praagh *et al.*, 1975). A variant of this situation in which ventriculo-arterial connexions are normal, but relations are again abnormal, has been termed 'isolated ventricular inversion' (Van Praagh and Van Praagh, 1966; Quero-Jimenez and Raposo-Sonenfeld, 1975). One of us has recently argued that both these situations should be classified as 'anatomically corrected malposition' (Anderson *et al.*, 1975a; Anderson and Wilkinson, 1975). It is



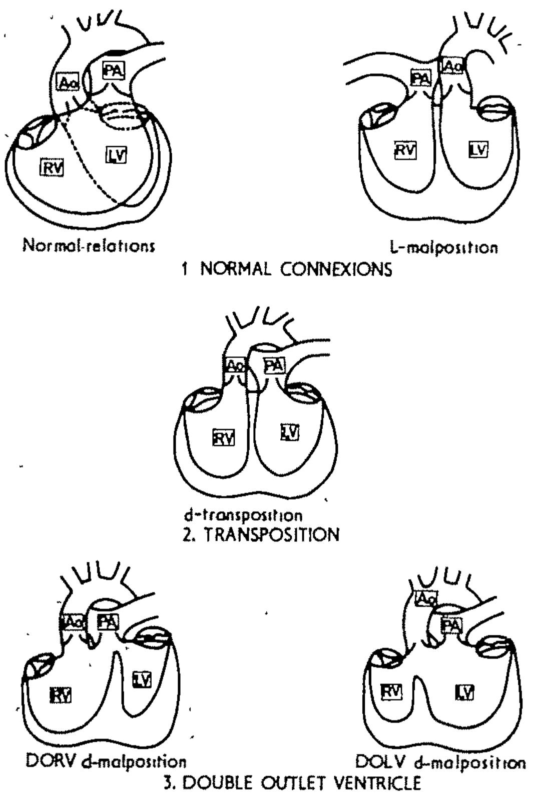
AMBIGUUS-d LOOP AMBIGUUS-L LOOP

FIG. 8 *Diagram illustrating the nomenclature in atrioventricular connexions in situs ambiguus. Since the atria either have the characteristics of two right or two left atria, concordance and discordance are not justifiable terms.*

now evident that such arguments are unnecessary if it is accepted that in all these instances the ventriculo-arterial *connexions* are normal. If this is established from the outset, then the abnormal relations can be specified as d- or l-malposition. (In all instances, the terms d- or l- as applied to a ventriculo-arterial connexion indicate the right or left spatial position of the aortic valve with regard to the pulmonary valve).

(ii) Transposition Transposition is present when both great arteries are placed across the septum so as to arise from morphologically inappropriate ventricles, the aorta from the right and the pulmonary artery from the left (or aorta from outlet chamber and pulmonary artery from primitive ventricle). Since primitive ventricle without outlet chamber does not possess a septum, all ventriculo-arterial connexions in these hearts fall into the double outlet category (see below). Since the term transposition describes the connexion, the terms d- or l- as applied to transposition are used to indicate the spatial relation of aortic to pulmonary valve, and convey no information regarding atrioventricular connexions. These would be described in our segmental nomenclature. The heart described as solitus-concordant-l-transposition would therefore have a left-sided aortic valve arising from the normally connected right ventricle. It would be a 'complete' transposition. In contrast, 'congenitally corrected' transposition would be described as solitus-discordant-l-transposition. In some circumstances the aortic valve may be directly in front of the pulmonary valve, and in these cases we would employ the term o-transposition (Squarcia, Ritter, and Kincaid, 1973). Another unusual form of transposition, in which the aorta is posterior, may be termed p-transposition (Van Praagh *et al.*, 1971; Wilkinson *et al.*, 1975).

(iii) Double outlet ventricle We have followed the precedent of Kirklin *et al.* (1973) and defined a double outlet connexion as that in which more than one and a half great arteries arise from the same ventricular or outlet chamber. A bilateral conus is not, therefore, a prerequisite for double outlet ventricle. It is well established that a continuum exists between normal connexions, double outlet ventricle, and transposition (Van Mierop and Wigglesworth, 1963; Lev *et al.*, 1972; Goor and Edwards, 1973; Anderson *et al.*, 1974b). Nowhere is this more apparent than in the situation where tetralogy of Fallot (considered by us to be a normal connexion) merges with double outlet right ventricle with pulmonary stenosis (solitus-concordant-DORV with d-malposition and pulmonary stenosis: Becker, Connor, and Anderson, 1975; Shinebourne, Anderson, and Bowyer, 1975). In this situation, we suggest that it is consistent to consider cases in which more than half the aorta arises from the right

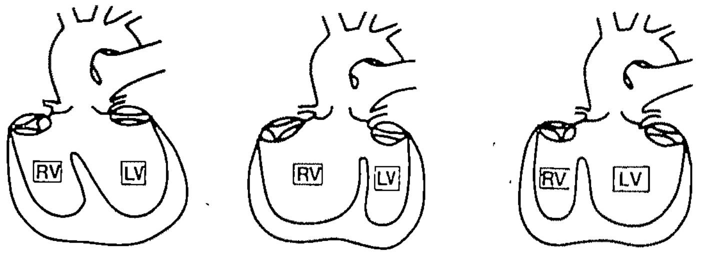


Normal-relations L-malposition
1 NORMAL CONNEXIONS

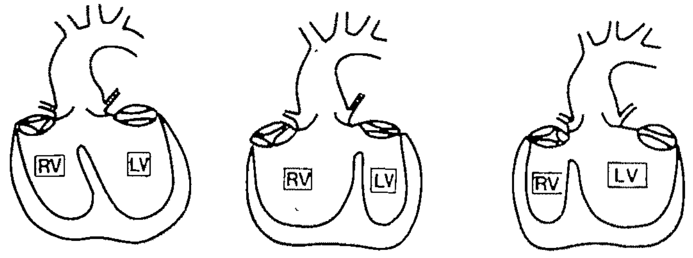
d-transposition
2. TRANSPOSITION

DORV d-malposition DOLV d-malposition
3. DOUBLE OUTLET VENTRICLE

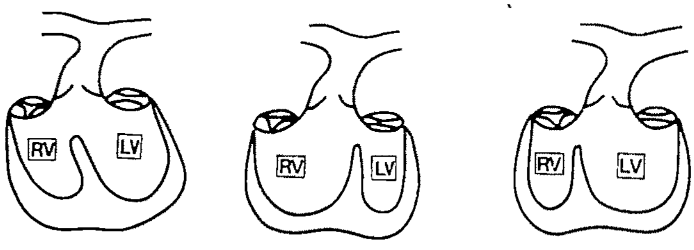
FIG. 9 *Diagrams illustrating ventriculo-arterial connexions. Though the great arteries are illustrated only in d-position for the second two categories, they can also exist in l-position (see text for discussion).*



Straddling From RV From LV
COMMON TRUNK



Straddling From RV From LV
SINGLE AORTIC TRUNK



Straddling From RV From LV
SINGLE PULMONARY TRUNK

FIG. 10 *Diagram illustrating the varieties of single arterial trunk. In addition to common truncus this category is required when the ventricular origin of either an atretic pulmonary artery or an atretic aorta cannot be identified: hence the categories single aortic trunk and single pulmonary trunk.*

ventricle as DORV irrespective of presence or absence of aortic-mitral fibrous continuity. Kirklin and Karp (1970) are inconsistent in this respect and continue to refer to such cases with aortic-mitral continuity as tetralogy. Likewise, arguments relative to the precise nature of the 'Taussig-Bing anomaly' (Taussig and Bing, 1949; Van Praagh, 1968; Hinkes, Rosenquist, and White, 1971) are resolved if connexions are considered rather than the state of the subpulmonary conus. Thus, if more than half the pulmonary artery arises from the right ventricle, the connexion is DORV irrespective of valvar continuity or discontinuity. If more than half is from the left ventricle it is transposition. When the artery directly overrides it is arbitrarily placed into one or other category (Kirklin *et al.*, 1973). The varying great arterial interrelations of DORV or DOLV are described as d-malposition or l-malposition.

As mentioned above, all ventriculo-arterial connexions in primitive ventricle without outlet chamber are examples of double outlet malposition, since there is only one ventricular chamber. For the purposes of diagnosis in this instance, the great arterial interrelations can be described as d-malposition or l-malposition, and the anterior or posterior position of the aorta indicated if necessary.

(iv) Single arterial trunk (Fig. 10). The single trunk can be a common truncus, an aorta, or a pulmonary artery, and each can arise from the morphological right ventricle, the morphological left ventricle, or in an overriding position. We specify single aortic trunk or a single pulmonary trunk when it is impossible to establish the origin of an atretic artery from the ventricles. This precludes the necessity of making paradoxical classifications such as 'double outlet right ventricle with pulmonary atresia' or of diagnosing 'transposition with pulmonary atresia' when it is not possible to determine if the pulmonary artery has indeed been placed across the septum. Positive identification of a common arterial trunk is made when coronary arteries and one or both pulmonary arteries arise from the ascending portion of the single arterial trunk.

D: Tabulate associated anomalies present (Table 2)

Any number of anomalies within each segment of the heart can accompany any possible combination of the above connexions. Tabulation and definition of all possibilities is not our present purpose. However, they can be conveniently grouped as (i) anomalies of venous return; (ii) anomalies of atrial anatomy; (iii) anomalies of the atrioventricular junction; (iv) anomalies of ventricular anatomy; (v) anomalies of corial anatomy and of the aortic arches and their derivatives.

E: Cardiac malpositions

Having specified connexions and anomalies within the heart, it may be considered desirable to specify the position of the heart within the chest, remembering that this conveys no information relevant to the internal cardiac anatomy or connexions. The heart may be within the right chest (dextrocardia), within the left chest (laevocardia), or centrally placed (mesocardia). Similarly, the apex of the heart may point to the left, right, or not be identifiable. Rotation of the heart about its long axis may also occur. If our nomenclature is used positional abnormalities of the heart within the chest will not affect interpretation of the anomaly (Anderson *et al.*, 1974a). In addition, it becomes apparent that terms such as dextrocardia, dextroversion, or dextrorotation add little to, or may confuse, understanding of the anomaly.

Discussion

It is of paramount importance to realize that a great difference exists between a connexion and a relation. A connexion automatically links two adjacent cardiac segments, whereas a relation does not, being more concerned with spatial orientation. To illustrate this point, in the variety of transposition known as posterior (p-) transposition (Van Praagh *et al.*, 1971; Wilkinson *et al.*, 1975), the arteries are normally related, i.e. the aorta is posterior and to the opposite side from the pulmonary artery with respect to the morphological left ventricle. However, the connexions are abnormal, the aorta arising from the right ventricle and the pulmonary artery from the left ventricle. Conversely, in anatomically corrected malposition the connexions are normal but the relations abnormal. In determining the course of blood through these hearts, it is the connexions which are important. It is in the emphasis on either connexions or relations that the two segmental approaches proposed on the one hand by Van Praagh (Van Praagh *et al.*, 1964a; Van Praagh, 1972) and on the other by de la Cruz and her colleagues (de la Cruz and Nadal-Ginard, 1972; de la Cruz *et al.*, 1974) differ so radically. The Van Praagh concept is based upon connexions throughout the heart. The de la Cruz hypothesis states atrioventricular connexions but is dependent on relations at ventriculo-arterial (or arterio-ventricular as described by these authors) level. This can be illustrated by reference to the categories of ventriculo-arterial connexions defined by Van Praagh (1973), namely transposition and double outlet ventricle. Within the connexions concept, these categories are discrete entities, and diagnosis of one category would exclude the other. In contrast, de la Cruz and her colleagues (1974) define the terms as relations. Thus, for them a double outlet ventricle can coexist with transposition if the aorta is in anterior position. They also use the terms 'concordant' and 'discordant' in an entirely different fashion from that proposed by Kirklin *et al.* (1973). For de la Cruz *et al.* (1974), an arterio-ventricular relation is concordant when the orientation of the great arteries can be used to predict the spatial relations and identities of the underlying ventricles. If a ventriculogram has been performed in order to establish this orientation, then this system is unnecessary, since the ventricle can be identified by morphological criteria and then used as a framework to establish ventriculo-arterial *connexions*. It is for this reason that we employ a concept based on connexions, and there is no doubt in our minds that such a scheme is superior to the alternative offered by de la Cruz and her colleagues (1972, 1974).

Kirklin and his colleagues' modification of the segmental approach of Van Praagh *et al.* (1971) was essentially one of using the terms 'concordant' and 'discordant' to express atrioventricular connexions (the terms having been introduced by Van Praagh *et al.*, 1964b) and extending their usage to ventriculo-arterial connexions. They indicated that both 'normal relations' and 'anatomically corrected malposition' could be considered as concordant ventriculo-arterial connexions, whereas transposition was a discordant connexion (Kirklin *et al.*, 1973). As we have indicated, one of us (R.H.A.) recently argued for the existence of anatomically corrected malposition as a discrete ventriculo-arterial relation, and further argued that 'isolated ventricular inversion' should be considered as the same relation (Anderson *et al.*, 1975a; Anderson and Wilkinson, 1975). However, such argument is unnecessary if it is realized that in all these relations the *connexions* are normal. We, therefore, recognize that the *connexions* between ventricles and arteries are of prime importance and that spatial relations and conal morphology are of secondary importance. We prefer the use of the terms 'normally connected', 'transposition', and 'double outlet ventricle' since we feel that use of 'concordant' and 'discordant' at both atrioventricular and ventriculo-arterial levels could lead to confusion (c.f. Kirklin *et al.*, 1973).

We have concentrated on connexions as our primary criteria and it has been necessary to demote in importance considerations of either spatial interrelations or conal morphologies. Thus, definition of transposition no longer requires the presence of subaortic conal musculature, as explained previously by Van Praagh *et al.* (1971). Similarly, we have followed the precedent of Kirklin *et al.* (1973) and do not insist upon the presence of bilateral conal musculature to define double outlet right ventricle. This concept for double outlet seems to us consistent with the approach to transposition, and more logical than that which insists upon presence of bilateral conal musculature. However, the latter definition is widely employed and has persuasive advocates (Baron, 1971). Choice of definitions is largely a matter of philosophy, but we would consider it inconsistent if we were to employ a 'connexions' approach while at the same time retaining a 'conal' definition for double outlet right ventricle. There are more practical reasons for adopting definitions based on ventricular connexions. It is often difficult using angiographic criteria to establish with certainty if a conus is present beneath a valve. Indeed, the distinction may not be possible following necropsy study, and to deal with this problem the subtle terms 'discontiNuity' and 'discontiGuity' have been introduced. Such niceties are unnecessary if connexions are the sole arbiter of how arteries are attached to their underlying ventricles.

In our terminology we have catered for exceptional situations where our original definitions are either paradoxical or ambiguous. This situation is present at the atrioventricular junction when either situs ambiguus is present, or two ventricular sinuses cannot be identified. In the first instance we used the terms d-loop and l-loop as proposed by Van Praagh *et al.* (1964a). We do not use these terms throughout because we consider them inferior to 'concordant' and 'discordant' when the latter terms can be properly employed. In the second instance, we have used the term 'primitive ventricle' to describe hearts in which the posterior interventricular septum is lacking. Problems of nomenclature concerning the univentricular heart are considerable (Harley, 1958; Van Praagh *et al.*, 1964a; de la Cruz and Miller, 1968; Lev *et al.*, 1969; Liberthson *et al.*, 1971; Macartney *et al.*, 1976). Many of the disagreements are the result of differing opinions regarding embryogenesis, and are therefore difficult to resolve. In terms of both nomenclature and surgical approach, the important feature of all these hearts, which by definition have absence of the posterior septum, is presence or absence of the anterior bulboventricular septum. This determines the presence or absence of an outlet chamber. The precise nature of the outlet and main chambers is of less importance, and as Lev *et al.* (1969) have indicated, whichever concept of embryogenesis is espoused the main ventricular chamber will always be the embryonic primitive ventricle. It is for this reason that we have adopted Lev's term 'primitive ventricle' and qualified it with regard to presence or absence of the outlet chamber. Our investigations indicate that hearts with atresia of an atrioventricular orifice can exist with the ventricular morphology of primitive ventricle, with or without outlet chamber (Anderson *et al.*, 1975b; Macartney *et al.*, 1976). We believe that exclusion of such hearts from the category of the univentricular heart is artificial (Van Praagh *et al.*, 1964a); Gasul, Arcilla, and Lev, 1966).

When the primitive ventricle possesses an outlet chamber, it also possesses an anterior bulboventricular septum. In these circumstances we have followed the precedent of Van Praagh *et al* (1971) and used definitions of ventriculo-arterial connexions as for the heart with right and left ventricles and an interventricular septum. In contrast, when primitive ventricle does not possess an outlet chamber it is composed of one chamber which always gives rise to both great arteries. In this situation, therefore, we have categorized arterial connexions as double outlet ventricle.

Another necessary alternative category is single arterial trunk. We have used this in an attempt to avoid paradoxical and semantically unsound definitions. In most instances in which there is either aortic or pulmonary atresia it is possible to identify the ventricular origin of the atretic artery using angiographic criteria. In these instances, we would categorize the connexion as if continuity were present and specify the atresia as an associated anomaly of the great arterial segment. However, where ventricular origin cannot be positively identified, then we believe it is more accurate to use the term 'single arterial trunk'.

In summary, we have outlined a concept of nomenclature and classification based upon the sequential identification of the cardiac chambers and their connexions. The concept is in essence a modification of that promoted by Van Praagh and his colleagues over the past decade (1964 to 1973). We accept that our presently employed definitions may require modification in the future. However, we contend that the system can cater for any heart as yet encountered and reported.

We are indebted to many of our colleagues for discussions leading up to the nomenclature presented. In particular, we thank Drs. James L. Wilkinson, Royal Liverpool Children's Hospital, and Anton E. Becker, Wilhelmina Gasthuis, Amsterdam. Our thoughts regarding this nomenclature were considerably influenced by lengthy discussions with Dr. John W. Kirklin of Birmingham, Alabama, and we are grateful to him for his help.

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Rules for diagnosis of arterioventricular discordances and spatial identification of ventricles

Crossed great arteries and transposition of the great arteries

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Rules are presented for the diagnosis of arterioventricular discordances and the spatial position of the ventricles in these cardiopathies by means of angiocardiography and the position of cardiac catheters. Because these rules are based on previous anatomo-embryological findings, the normal development of the conus and the truncus is briefly analysed. The probable morphogenesis of this group of truncoconal cardiopathies is discussed.

The fundamental process required to establish the diagnosis of these cardiopathies is as follows:

1) The truncoconal morphology is identified in the lateral projection. a) The anterior position of the pulmonary artery and its infundibulum with respect to the aorta and its infundibulum is characteristic of crossed great arteries with arterioventricular concordance or discordance. b) The anterior position of the aorta and its infundibulum with respect to the pulmonary artery and its infundibulum is characteristic of transposition of the great arteries with arterioventricular concordance or discordance.

2) Once the truncoconal morphology is identified, the use of the anteroposterior projection allows the establishment of the differential diagncsis between arterioventricular concordances and discordances, and of the spatial location of the ventricles in these entities. a) An anterior pulmonary artery directed from right to left, emerging from an infundibulum placed on the left side (anatomically right ventricle on the left) or an anterior pulmonary artery directed from left to right, arising from an infundibulum located to the right (anatomically right ventricular placed on the right), is the specific image of discordant crossed great arteries. b) An anterior pulmonary artery directed from right to left emerging from an infundibulum placed on the right side (anatomically right ventricle on the right side) or the anterior pulmonary artery directed from left to right arising from a left-sided infundibulum (anatomically right ventricle placed on the left side) is characteristic of concordant crossed great arteries. c) An anterior aorta placed to the right of the pulmonary artery and emerging from a left-sided infundibulum (anatomically right ventricle placed on the left side) or an anterior aorta placed to the left of the pulmonary artery and arising from an infundibulum placed on the right side (anatomically right ventricle placed on the right) is characteristic of discordant transposition of the great arteries. d) An anterior aorta placed to the right of the pulmonary artery emerging from a right-sided infundibulum (anatomically right ventricle placed on the right) or an anterior aorta placed to the left of the pulmonary artery arising from an infundibulum placed on the left (anatomically right ventricle placed on the left) is the specific picture of concordant transposition of the great arteries.

Reference is made to rules for the diagnosis of visceral situs and atrioventricular relations in order to determine whether the arterioventricular discordance corresponds to the variety with atrioventricular discordance or concordance.

Angiocardiographic postmortem studies of arterioventricular discordances and concordances are presented in support of the above considerations.

Arterioventricular discordances seem to have become more numerous as one reviews the published reports (de la Cruz *et al.*, 1974; Van Praagh *et al.*, 1975; Kirklin *et al.*, 1973; Shaffer *et al.*, 1967; Danielson *et al.*, 1972; Raghib, Anderson, and Edwards, 1966). Nevertheless they are still a small group among all the truncoconal cardiopathies.

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The purpose of this paper is to establish rules for the diagnosis of the different varieties of arterioventricular discordances and the spatial identification of the ventricles in this group of truncoconal malformations based on a previous paper (de la Cruz *et al.*, 1974) which was concerned with their anatomo-embryological interpretation and classification. A brief account of the rules for the diagnosis of the visceral situs and of the atrioventricular relations is also given, since this is indispensable in diagnosing precisely the variety of arterioventricular discordance (de la Cruz *et al.*, 1974). Reference is also made to the anatomical features and rules for the diagnosis of arterioventricular concordances (de la Cruz and Nadal-Ginard, 1972) in order to establish the differential diagnosis between this entity and arterioventricular discordances.

Postmortem studies are presented using contrast medium in the ventricles and the great arteries in specimens with crossed great arteries, and with transposition of the great arteries with arterioventricular discordance and with arterioventricular concordance.

Embryological considerations

The rules for the identification of the spatial position of the ventricles in patients with arterioventricular concordance (de la Cruz and Nadal-Ginard, 1972) or discordance with crossed great arteries or with transposition of the great arteries are based on the anatomical relation of the great arteries with the infundibulum of the anatomically right ventricle. This arterio-infundibular relation has been established on the basis of embryological concepts. Therefore, it is necessary to discuss briefly the normal development of the conus and the truncus and also the probable morphogenesis of transposition of the great arteries for which differing

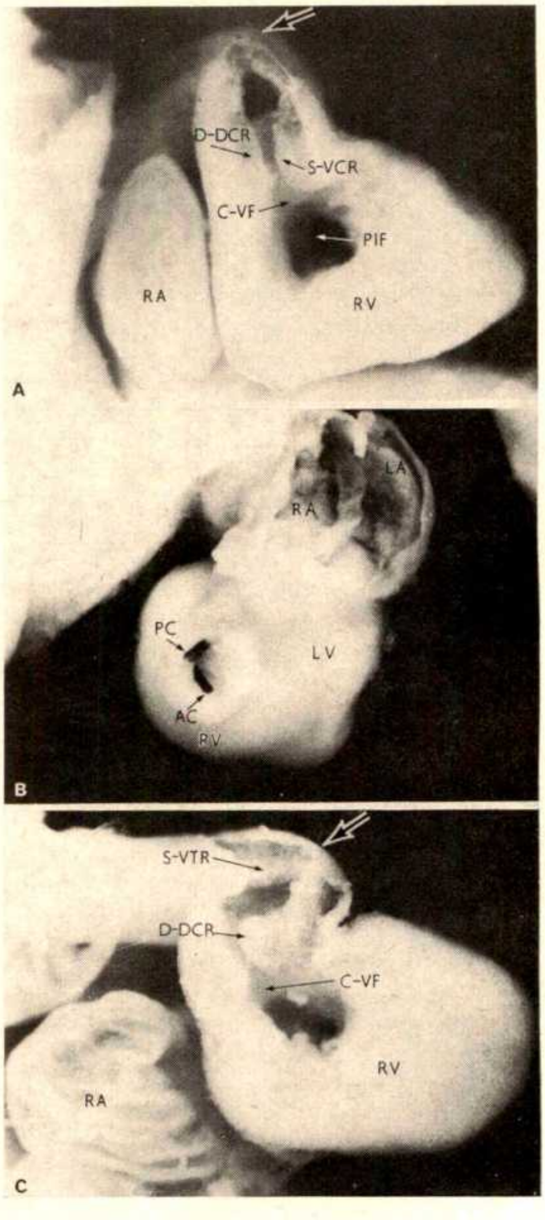

FIG. 1 *Microdissections of chick embryo hearts at stage 25 of Hamburger and Hamilton (4·5 to 5 days) which shows relations of both coni with primordium of the trabeculated region of the right ventricle and spatial orientation of truncoconal ridges. (A) Anterior and right wall of anterior conus and part of wall of primordium of trabeculated region of the right ventricle (RV) have been removed in order to show dextrodorsal conus ridge (D-DCR) and sinistroventral conus ridge (S-VCR) which separate anterior conus from posterior conus. Note posterior wall of posterior conus or conoventricular flange (C-VF) forming one edge of primary interventricular foramen (PIF). (B) Cross-section at level of both coni with two hairs, one is introduced in anterior conus (AC) and other in posterior conus (PC). Note spatial relation of both coni to each other and with respect to primordium of trabeculated region of right ventricle (RV). Both atria are continuous with left ventricle (LV). (C) Part of wall of truncus and of conus have been removed in order to show that dextrodorsal conus ridge (D-DCR) is continuous with sinistroventral truncus ridge (S-VTR) (×36).*

The white arrows indicate the truncoconal junction.

Key to abbreviations: RA, Right atrium. LA, Left atrium.

hypotheses have been presented (Van Praagh and Van Praagh, 1966; de la Cruz and da Rocha, 1956; Netter and Van Mierop, 1969).

The conus is the segment of the primary heart tube[1] situated between the truncus distally and the primordium of the trabeculated region of the right ventricle proximally (De Vries and Saunders, 1962). This portion of the primary heart tube has been variously designated: De Vries and Saunders (1962) call it 'infundibulum'; Kramer (1942), and Goor, Dische, and Lillehei (1972) call it 'conus'; Van Mierop *et al.* (1962) call it 'conus cordis', and Van Praagh and Van Praagh (1966) 'distal conus'.

De Vries and Saunders (1962), using descriptive embryology, established the early anatomical characteristics which permit the recognition of the conus and indicated that this structure appeared in Horizon XI of Streeter. The most relevant characteristics are its smooth walls which differ from those of the primordium of the trabeculated region of the right ventricle, with which it becomes continuous, and the presence of two conal ridges: a dextrodorsal and a sinistroventral one (Fig. 1A). These conal ridges divide the conus in an anterior and right-sided conus and a posterior and left-sided conus (Fig. 1A and B). Both coni are situated above the primordium of the trabeculated region of the anatomically right ventricle (Fig. 1A and B) (De Vries and Saunders, 1962; Van Mierop *et al.*, 1962; Kramer, 1942; de la Cruz, Muñoz-Armas, and Mũnoz-Castellanos, 1972). This is so, from the time of appearance of both coni in the Horizon XI of Streeter up to Horizon XVI of Streeter when the posterior conus is incorporated in the left ventricle (Van Mierop *et al.*, 1962) by an unknown developmental process. This has been shown by Gessner and Van Mierop (1970) using experimental embryological techniques in a beautiful experiment in which by preventing the incorporation of the posterior conus into the left ventricle both coni remained on the anatomically right ventricle, one of them anterior and right-sided and the other one, posterior and left-sided. When the posterior conus is incorporated in the left ventricle, the posterior wall of this conus (conoventricular flange) constituting one of the rims of the primary interventricular foramen (Fig. 1A and C) is reshaped and forms the infundibulum of the anatomically left ventricle, therefore establishing the fibrous continuity of this conus with the mitral valve. This is the process whereby the left ventricle acquires its outflow tract (Van Mierop *et al.*, 1962; de la Cruz *et al.*, 1972). The anterior conus remains in the anatomically right ventricle forming the infundibulum of this chamber (Van Mierop *et al.*, 1962; Netter and Van Mierop, 1969; Van Mierop, 1974; de la Cruz *et al.*, 1972). The posterior wall of the anterior conus, formed by the fused conus ridges, constitutes the horizontal portion of the crista supraventricularis and part of the definitive interventricular septum (Netter and Van Mierop, 1969; Van Mierop, 1974). The anatomically right ventricle is comprised, from the embryological point of view, of the anterior conus and the primordium of the trabeculated portion of the right ventricle. These structures give the right ventricle its distinctive features in the mature heart.

De Vries and Saunders (1962) describe the truncus as the distal segment of the primary heart tube, which is situated in the sagittal plane while the other segments are situated in the frontal plane. The truncus at its proximal end is continuous with the conus by means of an angular junction (Fig. 1A and C) where the semilunar valves of the great arteries will develop (De Vries and Saunders, 1962) and at its distal end with the aortic sac, by which it connects with the aortic arches. The truncus has two ridges: one is dextrodorsal (Kramer, 1942) or dextroinferior (De Vries and Saunders, 1962; Netter and Van Mierop, 1969) and the other sinistroventral (Kramer, 1942) or sinistrosuperior (De Vries and Saunders, 1962; Netter and Van Mierop, 1969). Kramer (1942), De Vries and Saunders (1962); Netter and Van Mierop (1969), and de la Cruz *et al.* (1972) have shown that the dextrodorsal conus ridge is continuous with the sinistroventral or sinistrosuperior truncus ridge, while the sinistroventral conus ridge is continuous with the dextrodorsal or dextroinferior truncus ridge. In this way the truncoconal ridges develop in a spiral fashion and when they fuse they constitute an equally spiral septum with a rotation of approximately 180 degrees in a clockwise direction if seen from the distal end (Fig. 1C).

The 4th aortic arch (horizontal portion of the aortic arch) joins the anterior and right portion of the distal end of the truncus, and the 6th aortic arch (branches of the pulmonary artery) joins its posterior and left portion. The development of the truncoconal septum in a spiral fashion causes the left and posterior 6th aortic arch (branches of the pulmonary artery) to communicate with the anterior conus (infundibulum of the anatomically right ventricle), while the anterior and right 4th aortic arch (horizontal portion of the aortic arch) communicates with the posterior conus (infundibulum of the anatomically left ventricle) (Fig. 2A). Thus, when the septation of the truncus is com-

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[1] Streeter (1945) considers the primary heart tube as that portion of the developing heart between the atrioventricular junction and the arterial arches.

pleted, it has been divided into two segments: one between the 6th aortic arch and the anterior conus, forming in the mature heart, the trunk of the pulmonary artery which crosses the aorta ventrally. The other segment is situated between the 4th aortic arch and the posterior conus; it gives origin to the ascending portion of the aorta of the mature heart which crosses the pulmonary arterial trunk posteriorly. This is the normal morphology of *crossed great arteries* (Fig. 2A).

The sigmoid aortic and pulmonary valve cusps originate in the wall of the truncus at the site of the conotruncal junction (De Vries and Saunders, 1962; Netter and Van Mierop, 1969). The two coronary sigmoid valve cusps of the aorta and the two posterior sigmoid valve cusps of the pulmonary artery originate from the ridges of the truncus while the non-coronary sigmoid valve cusp of the aorta and the anterior cusp of the pulmonary artery originate from the intercalar cushions.

Evidence obtained with techniques for descriptive and experimental embryology shows that the normal rotation of the truncoconal septum determines the normal morphology of crossed great arteries. These facts allow us to advance a hypothesis (de la Cruz and da Rocha, 1956), that the lack of rotation of the truncus septum will cause the branches of the pulmonary artery (6th aortic arch) which are posterior and left-sided to communicate by way of the pulmonary arterial trunk with the posterior conus. On the other hand, the horizontal portion of the aortic arch (4th aortic arch) which is anterior and right-sided will communicate with the anterior conus (infundibulum of the anatomically right ventricle) by way of the ascending portion of the aorta. This will cause the ascending portion of the aorta to be placed in a ventral position with respect to the trunk of the pulmonary artery (Fig. 2B). This anatomical arrangement constitutes our concept of *transposition of the great arteries*; it is for this reason that we do not include truncoconal morphologies with a posterior aorta or the side-by-side great arteries under this designation.

Transposition of the great arteries has two varieties. The most frequent one is seen with arterio-

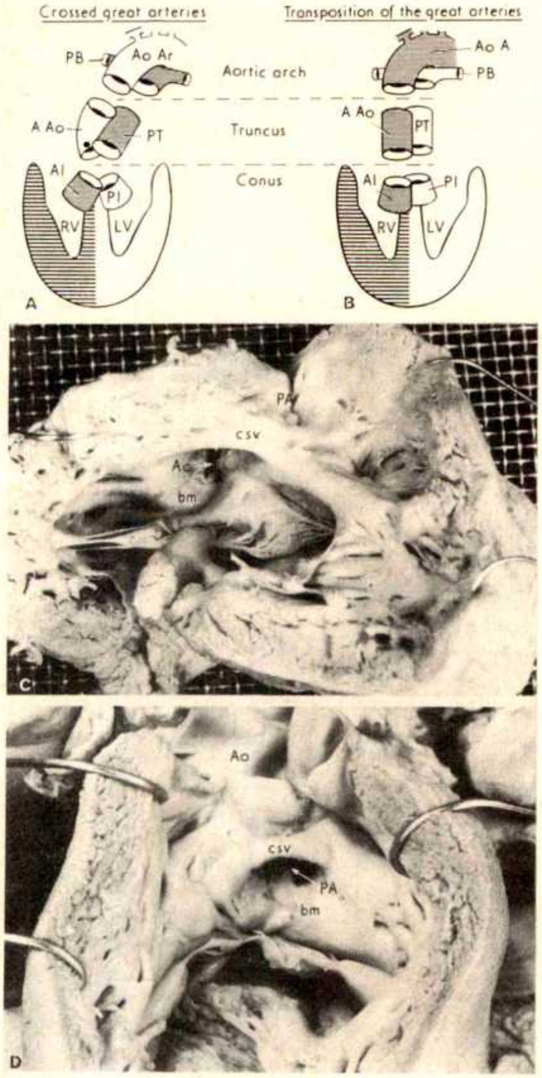

FIG. 2 *Relations of both great arteries with their infundibula in crossed great arteries and in transposition of great arteries. (A) Diagrammatic representation of relations of trunk of pulmonary artery (PT) and of ascending portion of aorta (AAo) in crossed great arteries. (B) Diagram of relations of ascending portion of aorta (AAo) with trunk of pulmonary artery (PT) in transposition of great arteries. (C) Specimen with crossed great arteries. Observe posterior aorta (Ao) with greater subaortic muscular mass (bm) with respect to pulmonary artery (PA) which has smaller muscular subpulmonary mass (CSV). (D) Anatomical specimen with transposition of great arteries. Observe posterior pulmonary artery (PA) with greater subpulmonary muscular mass (bm) than anterior aorta (Ao) which has smaller subaortic muscular mass (CSV).*

Key to abbreviations: bm, Bulbar muscle (posterior wall of posterior conus). CSV, Horizontal portion of crista supraventricularis (posterior wall of anterior conus). AoAr, aortic arch. PB, pulmonary branches. AI, anterior infundibulum. PI, posterior infundibulum. RV, right ventricle. LV, left ventricle.

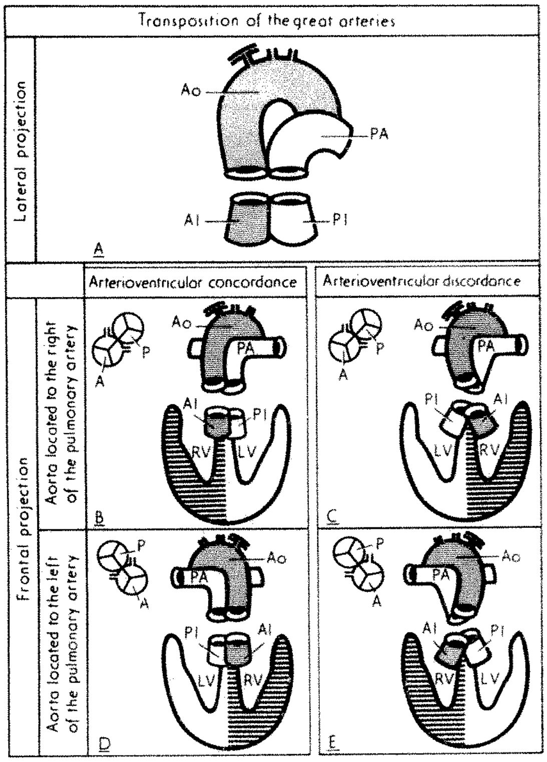
Transposition of the great arteries
Lateral projection
Ao
PA
AI
PI
A
Arterioventricular concordance
Arterioventricular discordance
Frontal projection
Aorta located to the right of the pulmonary artery
Aorta located to the left of the pulmonary artery
P
A
Ao
PA
AI
PI
RV
LV
B
C
D
E

FIG. 3 *Representative diagrams of relations of great arteries with their infundibula and with spatial location of ventricles in transposition of great arteries. (A) Diagram of lateral view in order to show anterior position of aorta and its infundibulum with respect to pulmonary artery and its infundibulum, which is general characteristic of transposition of great arteries. (B, C, D, and E) Frontal view depicting relation between ascending portion of aortic arch and anterior infundibulum which permits identification of spatial position of anatomically right ventricle. Diagram (B and D) shows that anterior aorta and its infundibulum placed on same side and parallel to pulmonary arterial trunk and its infundibulum are features which characterize concordant transposition of great arteries, while in C and E anterior aorta arising from an infundibulum placed on opposite side is distinctive feature of discordant transpositions of great arteries.*

Key to abbreviations: Ao, aorta; PA, pulmonary artery; AI, anterior infundibulum; PI, posterior infundibulum; RV, right ventricle; LV, left ventricle; A, aortic sigmoid valve cusps; P, pulmonary sigmoid valve cusps.

ventricular concordance and the least common one with arterioventricular discordance (de la Cruz *et al.*, 1974). Both originate on the basis of a non-rotated septum. In the variety with arterioventricular concordance the orientation of the truncus septum corresponds to the type of bulboventricular loop present, which determines the spatial position of the ventricles (de la Cruz *et al.*, 1974). Thus, a non-rotated truncus septum directed from right to left in a dorsoventral sense with a convex right-sided bulboventricular loop produces the anatomical picture characterized by an anterior and right-sided aorta with respect to the pulmonary arterial trunk and emerging from the anterior infundibulum on the right side (anatomically right ventricle on the right) (transposition of the great arteries with arterioventricular concordance) (Fig. 3B, 4C and 5C).

In the variety with arterioventricular discordance the orientation of the truncus septum does not correspond to the type of accompanying bulboventricular loop (de la Cruz *et al.*, 1974). Thus a non-rotated truncus septum directed from right to left in a dorsoventral sense, with a convex bulboventricular loop to the left, determines the anatomical picture characterized by an anterior and right-sided aorta with respect to the pulmonary artery and emerging from the anterior infundibulum situated on the left (anatomically right ventricle on the left side) (transposition of the great arteries with arterioventricular discordance) (Fig. 3C, 4D and 5D).

The great arteries and their valves originate from the truncus so that their reciprocal relation and that of their valvular planes will depend on the orientation of the truncus septum (de la Cruz *et al.*, 1974).

Crossed great arteries present as two varieties: with arterioventricular concordance which is the most frequent and with arterioventricular discordance, which is extremely rare (de la Cruz *et al.*, 1974). Both originate because of a rotated truncus septum, but in the variety with arterioventricular concordance the rotation of the septum corresponds with the type of accompanying bulboventricular loop (de la Cruz *et al.*, 1974). Thus, a truncus septum rotated in a clockwise manner is accompanied by a right-sided convexity of the bulboventricular loop, the anatomical expression of which is an anterior pulmonary artery directed from right to left which emerges from an anterior infundibulum situated on the right (anatomically right ventricle on the right). This occurs in the normal development of the heart (Fig. 6B, 7C, and 8C).

The variety with crossed great arteries and arterioventricular discordance arises because the rotation of the truncus septum does not correspond with the type of bulboventricular loop accompany-

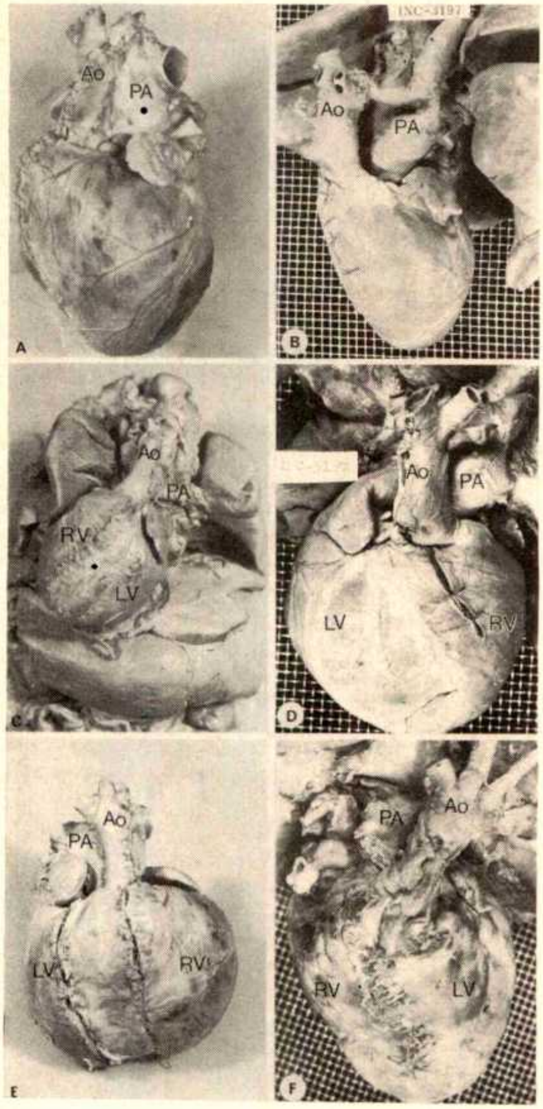

FIG. 4 *External view of anatomical specimens with concordant and discordant transposition of great arteries. Angiocardiographic studies of these specimens are seen in Fig. 5. (A) Lateral view of concordant transposition of great arteries and (B) discordant transposition of great arteries. Notice that in both types ascending portion of aortic arch is anterior with respect to trunk of pulmonary artery. (C) Concordant transposition of great arteries with ascending portion of aortic arch located to right of pulmonary arterial trunk. (D) Discordant transposition of great arteries with ascending portion of aortic arch placed on right side of pulmonary arterial trunk. (E) Concordant transposition of great arteries with ascending portion of aortic arch placed on left side of pulmonary arterial trunk. (F) Discordant transposition of great arteries with ascending portion of aortic arch placed on left side of pulmonary arterial trunk.*

Key to abbreviations: Ao, aorta; PA, pulmonary artery; RV, right ventricle; LV, left ventricle.

ing it (de la Cruz *et al.*, 1974). Thus, a septum with a clockwise rotation is accompanied by a left-sided convexity of the bulboventricular loop, which is expressed anatomically by an anterior pulmonary artery directed from right to left emerging from an anterior infundibulum located on the left (anatomically right ventricle on the left) (Fig. 6C, 7D and 8D).

The great arteries and their valves originate from the truncus (Netter and Van Mierop, 1969) for which reason their mutual relation and that of their valvular planes will depend on the clockwise or counterclockwise rotation of the truncus septum.

Van Praagh and Van Praagh (1966) indicate that during the normal development when both conuses appear, 'the presumptive aortic conus is right-sided, and the presumptive pulmonary conus is left-sided'. On the basis of this hypothesis he explains 'the normally related great arteries' as originating from an 'expansile growth of the pulmonary conus causing it to protrude anteriorly on the left side, carrying the pulmonary valve anteriorly, superiorly and to the left of the aortic valve, which remains posterior, inferior and relatively right-sided, in contact with the developing mitral valve' (Van Praagh and Van Praagh, 1966).

The findings of De Vries and Saunders (1962), Van Mierop *et al.* (1962), Netter and Van Mierop (1969), Van Mierop (1974), Kramer (1942), and de la Cruz *et al.* (1972) indicate that this process does not take place in the normal development of the truncus and of the conus. On the contrary, from the moment both conuses appear, when the conus ridges separating them are still not fused, the pulmonary conus is anterior and right-sided and the aortic conus is posterior and left-sided (Fig. 1A and B). Furthermore the aortic and pulmonary sigmoid valve cusps, which originate from the truncus, appear when the posterior conus has become incorporated into the anatomically left ventricle (de la Cruz *et al.*, 1972). On the other hand, the recent findings of Goor *et al.* (1972) indicating that both conuses are normally reabsorbed also argue against the hypothesis of a differential growth of the conus.

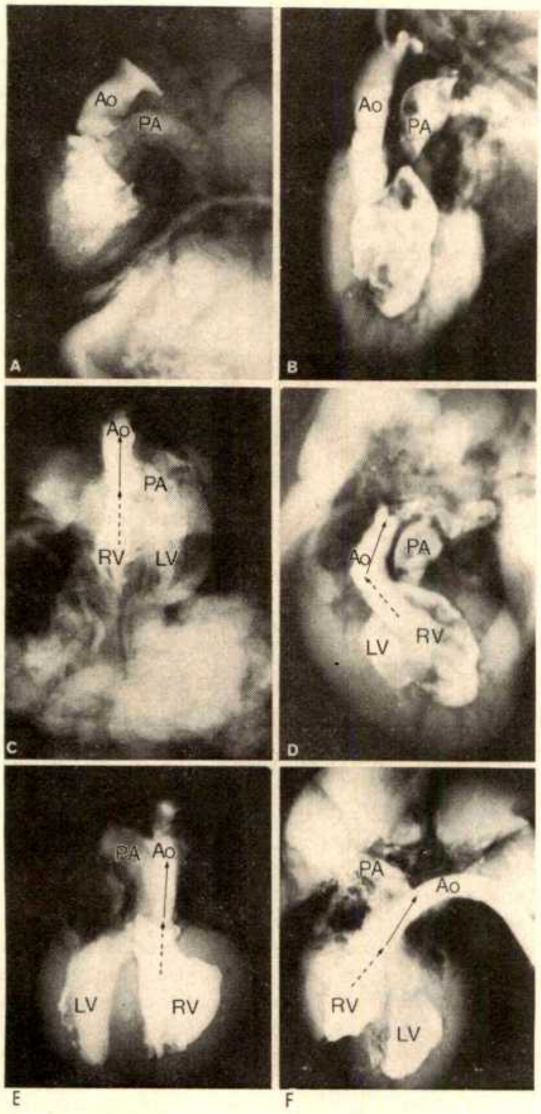

FIG. 5 *Angiocardiographic postmortem study of specimens with concordant and discordant transposition of great arteries. Lateral view of (A) concordant transposition of great arteries and (B) discordant transposition of great arteries both showing ascending portion of aortic arch and its infundibulum are anterior with respect to pulmonary artery trunk and its infundibulum which is general characteristic of transposition of great arteries. Frontal view of (C) concordant transposition of great arteries and (D) discordant transposition of great arteries. Notice in (C) that ascending portion of aortic arch is anterior and to right of pulmonary artery trunk and it arises from anterior infundibulum located on right side. This indicates that anatomically right ventricle is on right side, while in (D) ascending portion of aortic arch is also placed anteriorly and to right of pulmonary artery trunk but arises from anterior infundibulum located to left, and this indicates that anatomically right ventricle is placed on left side. Frontal view of (E) concordant transposition of great arteries and (F) discordant transposition of great arteries. Notice in (E) that ascending portion of aortic arch is anterior and placed on left side of pulmonary artery trunk and it arises from anterior infundibulum placed to left, all of which indicates that anatomically right ventricle is placed on left side, while in (F) ascending portion of aortic arch is also placed anteriorly and to left of pulmonary artery trunk but arising from anterior infundibulum placed on right side and this indicates that anatomically right ventricle is placed on right side. The dotted arrow indicates direction of infundibulum of anatomically right ventricle. Full arrow indicates direction of aorta.*

Key to abbreviations: Ao, aorta; PA, pulmonary artery; RV, right ventricle; LV, left ventricle.

This same hypothesis of a differential growth of the conus explains transposition of the great arteries as follows: 'following d-looping, the presumptive aortic conus is right-sided relative to the presumptive pulmonary conus (normal). Expansile growth of the aortic conus carries the developing aortic valve anteriorly and superiorly on the right side, relative to the pulmonary valve' (Van Praagh and Van Praagh, 1966). This hypothesis lacks solid support because it assumes that there are disturbances of some processes which do not exist in the normal development of the conus and the truncus.

These concepts go on to indicate that 'more important than the anatomic type of conus that is present (subpulmonary, subaortic, bilateral, absent) is the *amount* of conal musculature beneath each semilunar valve' (Van Praagh, 1973). These statements are often not supported by anatomical findings, since there are specimens of crossed great arteries with a larger amount of subaortic than of subpulmonary conal musculature (Fig. 2C) and specimens with transposition of the great arteries with a larger amount of subpulmonary conal than subaortic musculature (Fig. 2D).

We interpret the presence of the muscular posterior conus as a result of a developmental disorder in which the posterior wall of this conus instead of differentiating as happens normally into connective tissue, does so into muscular tissue.

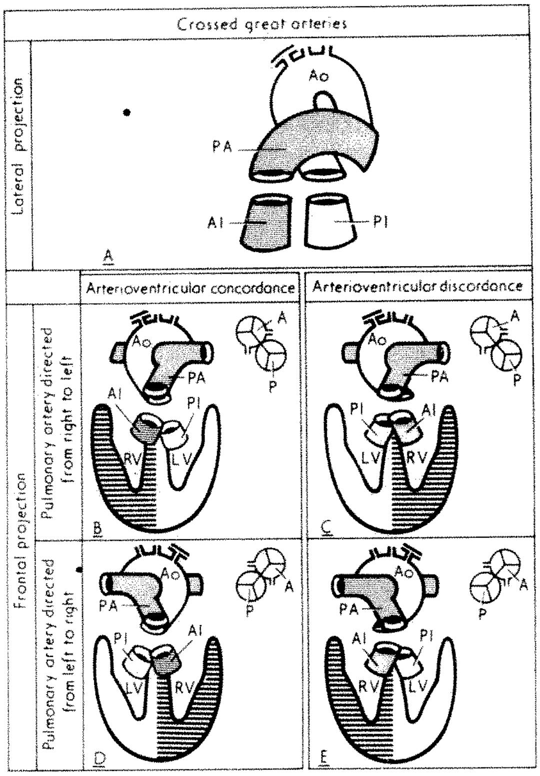
Crossed great arteries
Lateral projection
Ao
PA
AI
PI
A
Arterioventricular concordance
Arterioventricular discordance
Frontal projection
Pulmonary artery directed from right to left
Pulmonary artery directed from left to right
Ao
PA
AI
PI
RV
LV
A
P
B
C
D
E

FIG. 6 *Representative diagrams of relations of crossed great arteries with their infundibula and with spatial location of ventricles. (A) Diagram of lateral projection in order to show anterior position of pulmonary artery and its infundibulum with respect to aorta and its infundibulum, generally characteristic of crossed great arteries. (B, C, D, and E) Frontal projections show that relation between pulmonary artery trunk and anterior infundibulum permits identification of spatial position of the anatomically right ventricle. Diagram (B and D) indicates that anteriorly placed pulmonary artery arising from infundibulum located on opposite side is characteristic image of concordant crossed great arteries, while in (C and E) anterior pulmonary artery which arises from infundibulum placed on same side is characteristic feature of discordant crossed great arteries.*

Key to abbreviations: Ao, aorta; PA, pulmonary artery; AI, anterior infundibulum; PI, posterior infundibulum; RV, right ventricle; LV, left ventricle; A, aortic sigmoid valve cusps; P, pulmonary sigmoid valve cusps.

Independently of its histological structure, the posterior conus is the posterior infundibulum which is normally incorporated into the anatomically left ventricle. On the other hand, absence of a muscular anterior conus arises because the conus ridges (horizontal portion of the crista supraventricularis), which constitute the posterior wall of the anterior conus, differentiate into connective tissue instead of muscular tissue as it normally does. Therefore, despite its histological constitution the anterior conus is the infundibulum of the anatomically right ventricle. This is how we can interpret the presence of the semilunar atrioventricular fibrous continuity or discontinuity, on the basis of the process of differentiation of the cardiogenic mesenchyma without resorting to a differential growth process.

Diagnosis of truncoconal morphologies and spatial identification of ventricles

The diagnosis of arterioventricular discordances and concordances is made first of all by identifying the truncoconal morphology (Fig. 3A and 6A) and subsequently establishing the relations between the great arteries and their infundibula, which in turn permits the spatial identification of the ventricles (Fig. 3B to E and 6B to E).

It is indispensable in order to characterize and establish the differential diagnosis of arterioventricular discordances to refer to the rules for the diagnosis of arterioventricular concordances (de la Cruz and Nadal-Ginard, 1972).

A. Crossed great arteries

The truncoconal morphology of crossed great arteries, is *characterized essentially because the pulmonary artery trunk always has a ventral position with respect to the ascending portion of the aortic arch* (Fig. 6, 7, and 8), owing to the fact that the pulmonary artery emerges from the anterior infundibulum which is a region belonging to the anatomically right ventricle (Van Mierop *et al.*, 1962; Netter and Van Mierop, 1969; Van Mierop, 1974). This entity includes two groups: cases with arterioventricular concordance (Fig. 6A, B, D, 7A, C, E and 8A, C, E) and cases with arterioventricular discordance (Fig. 6A, C, E, 7B, D, F and 8B, D, F).

1. Concordant crossed great arteries (de la Cruz *et al.*, 1974) (Fig. 6A, B, D, 7A, C, E, and 8A, C, E). Within the group of crossed great arteries the concordant form is the most common. This group has the general features of crossed great arteries, i.e. *the pulmonary artery is ventral to the aorta and it arises from the anterior infundibulum (anatomically right ventricle)* (Fig. 6A, B, D; 7A, C, E, and 8A, C, E). The *distinctive feature* of this entity is that *the pulmonary artery and its infundibulum (anterior infundibulum) has the same direction*

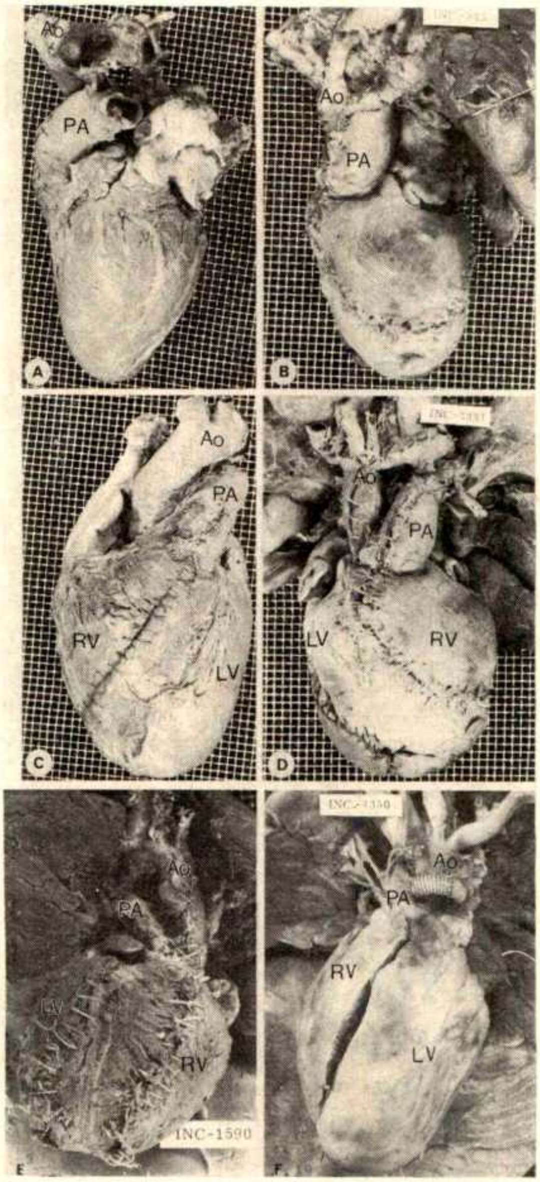

FIG. 7 *External view of anatomical specimens of concordant and discordant crossed great arteries. Angiographic studies of these specimens are shown in Fig. 8. (A) Lateral view of case of concordant crossed great arteries and (B) of discordant crossed great arteries. Notice that in both pulmonary artery trunk is anterior with respect to ascending portion of aortic arch. (C) Concordant crossed great arteries with pulmonary artery trunk directed from right to left. (D) Discordant crossed great arteries with pulmonary artery trunk directed from right to left. (E) Concordant crossed great arteries with pulmonary artery trunk directed from left to right. (F) Discordant crossed great arteries with pulmonary artery trunk directed from left to right.*

Key to abbreviations: Ao, aorta; PA, pulmonary artery; RV, right ventricle; LV, left ventricle.

and orientation; the same is true of the aorta and its infundibulum (de la Cruz and Nadal-Ginard, 1972) (Compare B, D with C, E in Fig. 6 and C, E with D, F in Fig. 8).

The clinical diagnosis is made fundamentally by means of the radiological study of the position of cardiac catheters in the lateral and anteroposterior projections and with biplane angiocardiography. In the *lateral projection the anterior position of the pulmonary artery and its infundibulum with respect to the aorta is confirmed* (crossed great arteries) (Fig. 8A). With the *anteroposterior projection* the fact can be established that *the pulmonary artery and its infundibulum follow the same spatial direction (crossed great arteries with arterioventricular concordance)* (Fig. 8C and E). Because the pulmonary artery emerges from the anterior infundibulum which corresponds to the anatomical right ventricle, the relation of the pulmonary artery trunk and its infundibulum allows identification of the spatial position of the anatomically right ventricle. Thus, when the pulmonary artery and its infundibulum are directed from right to left it means that the anatomically right ventricle is placed on the right side (Fig. 6B and 8C), whereas if the pulmonary artery and its infundibulum are directed from left to right, this indicates that the anatomically right ventricle is placed on the left side (de la Cruz and Nadal-Ginard, 1972) (Fig. 6D and 8E).

2. Discordant crossed great arteries (de la Cruz *et al.*, 1974) (Fig. 6A, C, E, 7B, D, F and 8B, D, F). Crossed great arteries with arterioventricular discordance (discordant crossed great arteries) have, therefore, the general features of crossed great arteries, i.e. *the pulmonary artery is ventral to the aorta and it arises from the anterior infundibulum* (anatomically right ventricle) (Fig. 6A, C, E, 7B, D, F and 8B, D, F). *The distinctive feature* in this group is that *the pulmonary artery and its infundibulum (anterior infundibulum) do not have the same spatial direction, the same is true of the aorta and its infundibulum.* (Compare C, E with B, D in Fig. 6 and D, F with C, E in Fig. 8.)

This group is diagnosed with the same laboratory techniques as the previous group, first confirming the diagnosis *of crossed great arteries in the lateral angiocardiogram, i.e. anterior position of the pulmo-*

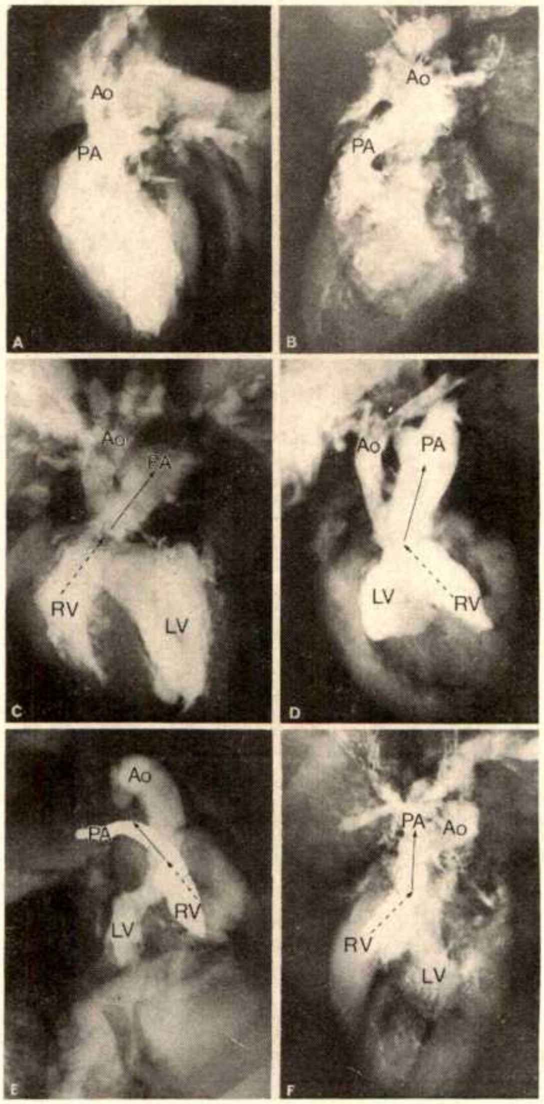

FIG. 8 *Angiocardiographic postmortem study of specimens of concordant and discordant crossed great arteries. (A) Lateral view of concordant crossed great arteries and (B) of discordant crossed great arteries. Both show pulmonary artery trunk and infundibulum anteriorly placed with respect to aorta and its infundibulum which is a general characteristic of crossed great arteries. (C) Frontal view of concordant crossed great arteries and (D) discordant crossed great arteries. Observe (C) that the pulmonary artery trunk, which is anterior, is directed from right to left and originates from an anterior infundibulum located on right, which indicates that anatomically right ventricle is placed on right, while in (D) the pulmonary artery trunk also directed from right to left but originating from an anterior infundibulum located to left, indicates that the anatomical right ventricle is placed on left side. (E) Frontal view of concordant crossed great arteries and (F) discordant crossed great arteries. Observe in (E) that the anteriorly placed pulmonary artery trunk directed from left to right arising from an anterior infundibulum placed on left side, indicates that the anatomical right ventricle is placed on the left, while in (F), the pulmonary artery trunk is also directed from left to right but arising from an anterior infundibulum placed on the right side indicates that the anatomically right ventricle is placed on the right side. Dotted arrow indicates direction of infundibulum of the anatomically right ventricle. Full arrow indicates direction of pulmonary artery.*

Key to abbreviations: Ao, aorta; PA, pulmonary artery; RV, right ventricle; LV, left ventricle.

nary artery and its infundibulum with respect to the aorta (Fig. 8B) and then analysing the *frontal or anteroposterior projection* in order to establish the fact that *the pulmonary artery trunk and its infundibulum do not follow the same spatial direction* (crossed great arteries with arterioventricular discordance) (Fig. 8D and F). Because the pulmonary artery arises from the anterior infundibulum which corresponds to the anatomically right ventricle, the relation between the trunk of the pulmonary artery and its infundibulum allows the identification of the spatial position of the anatomically right ventricle. If, for instance, the pulmonary artery is directed from right to left and it emerges from a left-sided infundibulum, it indicates that the anatomically right ventricle is placed on the left side (Fig. 6C and 8D), while if the pulmonary artery is directed from left to right arising from a right-sided infundibulum, the anatomically right ventricle must be placed on the right side (Fig. 6E and 8F).

There are two anatomical varieties within this group depending on the direction of the pulmonary artery trunk and its infundibulum (de la Cruz *et al.*, 1974). The anatomical image of the variety with pulmonary artery directed from right to left emerging from a left-sided infundibulum which in turn is directed from left to right in a caudo-cranial sense is characterized by the fact that the pulmonary artery trunk and its infundibulum form a curve convex to the right and concave to the left. This curve is ventrally placed with respect to the curve formed by the aorta and its infundibulum, which in turn is concave to the right and convex to the left

(Fig. 6C and 8D). The entire image is that of an X whose two left limbs formed by the pulmonary artery trunk and the infundibulum of the anatomically right ventricle placed on the left side overlap the two right limbs of the X at the level of the valvular floors. The right limbs in turn are formed by the ascending portion of the aortic arch and the infundibulum of the anatomically left ventricle placed on the right side (Fig. 6C, 7D, and 8D). The reciprocal relation of the valvular floors of the great arteries is that observed when the pulmonary artery is directed from right to left in cases of concordant crossed great arteries (de la Cruz *et al.*, 1974) (Compare C with B in Fig. 6).

The variety with the pulmonary artery directed from left to right emerging from an infundibulum placed on the right side, which in turn is directed from right to left in a caudo-cranial sense is characterized by the pulmonary artery trunk and its infundibulum form a curve concave to the right and convex to the left. This curve is placed ventrally with respect to the curve formed by the ascending portion of the aortic arch and its infundibulum which is concave to the left and convex to the right (Fig. 6E and 8F). In this variety the right limbs of the X, formed by the pulmonary artery trunk and the infundibulum of the anatomically right ventricle placed on the right side also overlap the two left limbs of the X at the level of the valvular planes. Those limbs are constituted by the ascending portion of the aortic arch and the infundibulum of the anatomically left ventricle placed on the left (Fig. 6E, 7F, and 8F). The reciprocal relation of the valvular floors of the aorta and the pulmonary artery is that which corresponds to that seen when the pulmonary artery is directed from left to right in concordant crossed great arteries (de la Cruz *et al.*, 1974) (Compare E with D in Fig. 6).

B. Transposition of the great arteries

The truncoconal morphology of *transposition of the great arteries is characterized essentially by the fact that the ascending portion of the aortic arch always has a ventral position with respect to the pulmonary artery* (Fig. 3, 4 and 5) *since the aorta emerges from the anterior infundibulum* (de la Cruz and da Rocha, 1956) *(anatomically right ventricle)*. This entity includes two groups: one with arterioventricular concordance (Fig. 3A, B, D, 4A, C, E and 5A, C, E) and one with arterioventricular discordance (Fig. 3A, C, E, 4B, D, F and 5B, D, F).

1. Concordant transposition of the great arteries

1. Concordant transposition of the great arteries (De la Cruz *et al.*, 1974) (Fig. 3A, B, D, 4A, C, E and 5A, C, E). Within the group of transposition of the great arteries the concordant form occurs most often. This type has the general features of transposition of the great arteries, i.e. *the ascending portion of the aortic arch is ventrally placed with respect to the trunk of the pulmonary artery* and it arised from the anterior infundibulum (anatomically right ventricle) (Fig. 3A, B, D, 4A, C, E and 5A, C, E). The distinctive feature in this entity is that *the ascending portion of the aortic arch and its infundibulum (anterior unfundibulum) are placed on the same side in the frontal plane and parallel to the pulmonary artery trunk and its infundibulum* (de la Cruz and Nadal-Ginard, 1972) (Compare B, D with C, E in Fig. 3 and C, E with D, F in Fig. 5).

The clinical diagnosis is made with the radiological study of the position of cardiac catheters in the lateral and anteroposterior projections and by the use of biplane angiocardiography. The *lateral projection* confirms *the anterior position of the aorta and its infundibulum with respect to the pulmonary artery* (transposition of the great arteries) (Fig. 5A); with the *anteroposterior projection* the fact is established that the *aorta and its infundibulum are placed on the same side in the frontal plane and parallel to the pulmonary artery and its infundibulum* (transposition of the great arteries with arterioventricular concordance) (Fig. 5C and E). Because of the fact that the aorta emerges from the anterior infundibulum which corresponds to the anatomically right ventricle, the relation of the ascending portion of the aortic arch and its infundibulum allows the identification of the spatial position of the anatomically right ventricle. Thus, when the aorta and its infundibulum are placed to the right of the pulmonary artery and its infundibulum it indicates that the anatomically right ventricle is placed on the right (anterior infundibulum to the right) (Fig. 3B and 5C), whereas if the aorta and its infundibulum are placed to the left of the pulmonary artery and its infundibulum, it indicates that the anatomically right ventricle is placed on the left (anterior infundibulum on the left side) (de la Cruz and Nadal-Ginard, 1972) (Fig. 3D and 5E).

2. Discordant transposition of the great arteries (de la Cruz *et al.*, 1974) (Fig. 3A, C, E, 4B, D, F and 5B, D, F). Transpositions of the great arteries with arterioventricular discordance present the general features *of transposition of the great arteries, i.e. the ascending portion of the aortic arch is anteriorly placed with respect to the pulmonary artery trunk and it arises from the anterior infundibulum* (anatomically right ventricle) (Fig. 3A, C, E, 4B, D, F and 5B, D, F). The feature peculiar to this group *is* the fact that *the ascending portion of the aorta emerges from the anterior infundibulum placed on the* *opposite side in the frontal plane* (compare C and E with B and D in Fig. 3 and D and F with C and E in Fig. 5). In this group the diagnosis is made with the same techniques described above, first corroborating the diagnosis of *transposition of the great arteries by the anterior position of the aorta and its infundibulum with respect to the pulmonary artery in the* lateral projection (Fig. 5B) and then determining in the *anteroposterior projection* that *the ascending portion of the aortic arch arises from an infundibulum placed on the opposite side in the frontal plane* (transposition of the great arteries with arterioventricular discordance) (Fig. 5D and F). Owing to the fact that the aorta emerged from the anterior infundibulum which corresponds to the anatomically right ventricle, the relation of the ascending portion of the aortic arch and its infundibulum enables identification of the spatial position of the anatomically right ventricle. Thus, if the aorta is placed on the right side of the pulmonary artery and it emerges from an infundibulum placed on the left side, it indicates that the anatomically right ventricle is placed on the left side (Fig. 3C and 5D), whereas if the aorta is placed on the left side of the pulmonary artery and it arises from an infundibulum located on the right side, it indicates that the anatomically right ventricle is placed on the right side (Fig. 3E and 5F).

This group comprises two anatomical varieties which depend on the position of the aorta and its infundibulum (de la Cruz *et al.*, 1974). The anatomical variety with a right-sided aorta is characterized because the aorta placed on the right of the pulmonary artery is continuous with the anterior infundibulum placed on the left side which is directed from left to right in a caudo-cranial sense (anatomically right ventricle placed on the left) (Fig. 3C and 5D), while the pulmonary artery is placed behind and to the left of the aorta, and it emerges from a posterior infundibulum placed on the right side and directed from right to left in a caudo-cranial sense (anatomically left ventricle placed on the right side) (Fig. 3C and 5D). The reciprocal relation of the valvular planes of the great arteries is that seen when the aorta is placed on the right side of the pulmonary artery in transposition of the great arteries (de la Cruz *et al.*, 1974) (Compare C with B in Fig. 3).

The anatomical variety with the aorta placed on the left side of the pulmonary artery is characterized by the aorta being continuous with the anterior infundibulum which is placed on the right side and directed from right to left in a caudo-cranial sense (anatomically right ventricle placed on the right side) (Fig. 3E and 5F), whereas the pulmonary artery is placed behind and to the right of the aorta, and it emerges from the posterior infundibulum which is placed on the left side and directed from left to right in a caudo-cranial sense (anatomically left ventricle placed on the left) (Fig. 3E and 5F). The reciprocal relation of the valvular planes of the great arteries is that seen in transposition of the great arteries with the aorta placed on the left side of the pulmonary artery (de la Cruz *et al.*, 1974) (compare E with D in Fig. 3).

The rules to locate the ventricle by the analysis of the truncoconal morphologies in arterioventricular discordances are valid, as in arterioventricular concordances (de la Cruz *et al.*, 1974), whether the two great arteries emerge from the anatomically right ventricle or one artery arises from one ventricle and the other overrides or else when both arteries arise from the anatomically left ventricle.

In a previous paper one of us (de la Cruz *et al.*, 1974) had maintained that the ventricular cavities could not be located spatially in arterioventricular discordances with crossed great arteries or with transposition of the great arteries, following the rules established for the identification of these cavities in arterioventricular concordances. This fact remains true. However, the ventricular cavities can be identified in arterioventricular discordances applying the specific rules established in this paper for the diagnosis of these malformations.

The rules for the spatial location of the ventricles in transposition of the great arteries with arterioventricular concordance or discordance, are not applicable to the 'anatomically corrected transposition' because this malformation, by our definition, is not a transposition of the great arteries.

Van Praagh *et al.* (1971) also conclude that anatomically corrected transposition must be excluded from the group of transposition of the great arteries, 'because transposition in fact is not present', and he designates it as 'anatomically corrected malposition'. In a previous paper we indicated (de la Cruz *et al.*, 1974) that anatomically corrected transposition is a partial distorsion of the great arteries with arterioventricular discordance, for which reason the rules for spatial identification of the ventricles in cases of crossed great arteries with arterioventricular concordance or discordance are not applicable either.

Diagnosis of visceral situs

Arterioventricular discordances, as well as arterioventricular concordances may occur in situs solitus or in situs inversus. The diagnosis of the visceral situs is established identifying the spatial position of the hepato-cavo-atrial complex, formed by the

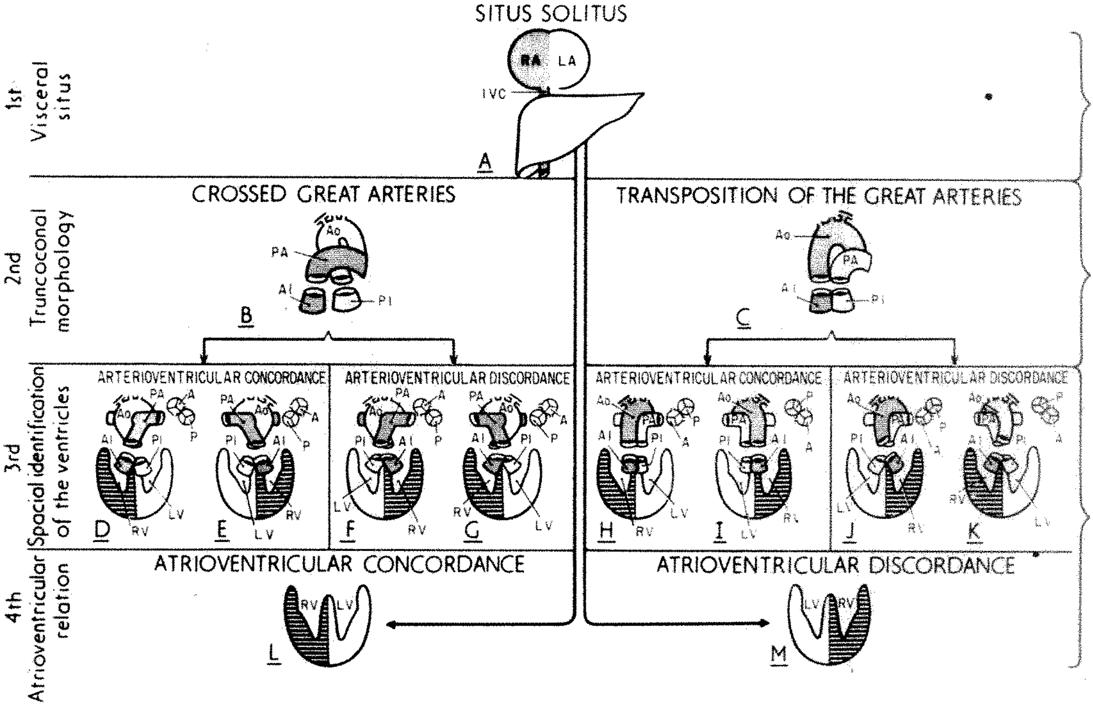
SITUS SOLITUS
RA
LA
IVC
A
1st Visceral situs
2nd Truncoconal morphology
3rd Spacial identification of the ventricles
4th Atrioventricular relation
Frontal
Lateral
Frontal
CROSSED GREAT ARTERIES
TRANSPOSITION OF THE GREAT ARTERIES
Ao
PA
AI
PI
B
C
ARTERIOVENTRICULAR CONCORDANCE
ARTERIOVENTRICULAR DISCORDANCE
ARTERIOVENTRICULAR CONCORDANCE
ARTERIOVENTRICULAR DISCORDANCE
A
P
RV
LV
D
E
F
G
H
I
J
K
ATRIOVENTRICULAR CONCORDANCE
ATRIOVENTRICULAR DISCORDANCE
L
M

FIG. 9 *Representative diagram depicting sequence that should be followed in order to establish differential diagnosis between crossed great arteries and transposition of great arteries and also of different varieties of these two entities. (A) Characteristics of situs solitus. (B and C) Differential signs between crossed great arteries and transposition of great arteries. (D, E, F, G, H, I, J, and K) Characteristics of arterioventricular concordances and discordances in crossed great arteries and in transposition of great arteries and spatial location of ventricles. Relation expressed by arrow between (L and M) with (A) allows specification of presence of atrioventricular concordance or discordance.*

Key to abbreviations: Ao, aorta; PA, pulmonary artery; AI, anterior infundibulum; PI, posterior infundibulum; RV, right ventricle; LV, left ventricle; A, aortic sigmoid valve cusps; P, pulmonary sigmoid valve cusps; RA, right atrium; LA, left atrium; IVC, inferior vena cava.

large lobe of the liver, the suprahepatic portion of the inferior vena cava, and the anatomically right atrium independently of the position of the other segments of the heart and the rest of the viscera (de la Cruz and Nadal-Ginard, 1972). The identification of the anatomically right atrium is made by identifying radiologically the position of the catheter in the suprahepatic segment of the inferior vena cava or with angiocardiography.

The diagnosis of situs solitus is made when the hepato-cavo-atrial complex is placed on the right side and that of situs inversus when this anatomical complex is placed on the left side.

The cardiac apex may have three different directions in each situs. In situs solitus the apex is directed to the left (normally placed heart), medial apex (mesocardia), and apex to the right (dextroversion). In situs inversus there may be a right-sided apex (mirror-image dextrocardia), a medial apex (mesocardia), or an apex directed to the left (laevoversion) (Anselmi *et al.*, 1972).

Diagnosis of atrioventricular relation

Arterioventricular discordances, like arterioventricular concordances, may present with atrioventricular concordance or atrioventricular discordance (de la Cruz *et al.*, 1974).

Atrioventricular concordances are characterized by the anatomically right atrium and the anatomically right ventricle being placed in the same side in space, independently of their position within the chest. In situs solitus both are on the right and in situs inversus both are on the left. Atrioventricular discordances are characterized by the fact that the anatomically right atrium and the anatomically left ventricle are placed spatially on the same side independently of their position within the chest. In situs solitus both are placed on the right and in situs inversus both are placed on the left side.

The diagnosis of atrioventricular concordance or discordance is made following this sequence: 1) The situs is identified by a radiological study in order to locate the hepato-cavo-atrial anatomical complex in space. 2) The truncoconal morphology is identified. 3) The diagnosis of arterioventricular discordance or concordance is made, which in turn permits the spatial identification of the ventricles in these entities. 4) The spatial relation is established between the atria and the ventricles (Fig. 9).

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Catheter mapping of retrograde atrial activation

Observations during ventricular pacing and AV nodal re-entrant paroxysmal tachycardia[1]

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A systematic study of retrograde atrial activation sequence at commonly used electrode catheter recording sites in 8 patients without, and in 4 patients with AV nodal re-entrant paroxysmal tachycardia was made. During right ventricular pacing, the retrograde atrial activation sequence was low septal right atrium—proximal coronary sinus—distal coronary sinus—high right atrium. During the episodes of paroxysmal tachycardia, a similar pattern was observed. This information should be helpful in the understanding of abnormal activation sequences in patients with paroxysmal supraventricular tachycardia in whom retrogradely conducting anomalous pathways are suspected.

Electrophysiological studies in the catheterization laboratory have contributed significantly to the understanding of mechanisms of paroxysmal supraventricular tachycardia. One group of patients with paroxysmal tachycardia is characterized by the presence of anomalous pathways, either manifest or concealed (Durrer and Wellens, 1974; Coumel and Attuel, 1974; Spurrell, Krikler, and Sowton, 1974a; Neuss, Schlepper, and Thorman, 1975; Zipes, DeJoseph, and Rothbaum, 1974). In these patients, the anomalous pathway usually constitutes the retrograde limb of an atrioventricular circus movement during paroxysmal tachycardia. Documentation of the presence of a retrogradely conducting anomalous pathway is dependent upon demonstration of abnormal retrograde activation sequences, during both ventricular pacing and paroxysmal tachycardia (Wellens and Durrer, 1974; Svenson *et al.*, 1974; Wellens, 1975; Denes *et al.*, 1975; Gallagher *et al.*, 1975). For example, retrograde activation of the atria via a left lateral Kent bundle should produce early activation of the left atrium, as recorded from a catheter placed in the distal coronary sinus.

Despite the obvious usefulness of catheter electrode atrial mapping during retrograde activation, there has been no systematic study of normal retrograde activation via the His bundle and AV node, with commonly used electrode catheter recording sites. Without a clear picture of what normal activation is like, demonstration of 'abnormal sequences' is of questionable meaning. In this study we have attempted to define the normal pattern of retrograde activation of the atria with commonly used catheter electrode positions in patients with and without AV nodal re-entrant paroxysmal tachycardia. This information should be extremely helpful in analysis of patients with paroxysmal tachycardia in whom retrogradely conducting anomalous pathways are suspected.

Methods

The study group consisted of 12 patients with intact AV conduction undergoing electrophysiological evaluation. Group 1 consisted of 8 patients with suspected or proven conduction disease, who were classified as having normal VA conduction. These patients fulfilled the following criteria: 1) no previous history of palpitations or paroxysmal tachycardia; 2) absence of manifest antegrade pre-excitation determined by the evaluation of standard 12-lead electrocardiograms; 3) evidence of retrograde AV nodal conduction (without evidence of retrograde

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TABLE 1 *Clinical, electrocardiographic, and electrophysiological findings in 12 patients*

Case No.	*Age (yr)*	*Sex*	*Clinical diagnosis*	*Electrocardiogram*		*Electrophysiological findings during sinus rhythm (ms)*							
				PR(s)	*QRS(s)*	*HR*	*PA*	*AH*	*HV*	*FRP-AVN*	*ERP-AVN*	*FRP-A*	*ERP-A*
Group 1													
1	24	M	NHD	0·14	0·08	81	38	92	55	660	630	400	380
2	57	M	VHD	0·16	0·08	62	45	79	47	400	320	300	220
3	63	M	SSS	0·20	0·08	86	42	96	50	530	400	300	210
4	52	M	ASHD	0·14	0·08 (LVH)	92	44	89	40	390	<360	360	290
5	34	F	Sarcoidosis	0·14	0·08	97	35	87	34	320	<250	250	230
6	57	M	ASHD	0·16	0·08	53	43	120	40	450	340	340	240
7	64	M	ASHD	0·18	0·12 (RBBB & LASH)	90	42	76	86	330	<310	310	280
8	81	M	ASHD	0·24	0·12 (RBBB & LASH)	64	59	145	65	665	450	280	230
Group 2													
9	25	F	NHD	0·14	0·08	91	41	58	35	S=545 F=340	S=<250 F= 260	250	180
10	53	M	ASHD	0·18	0·08 (LVH)	99	26	122	54	S=470 F=410	S=<310 F= 350	310	280
11	55	M	NHD	0·16	0·08	62	40	87	55	S=520 F=425	S= 285 F= 350	260	240
12	77	M	HCVD	0·16	0·08 (LVH)	96	50	91	49	S=440 F=330	S=<250 F= 280	250	180

Abbreviations NHD=No organic heart disease; VHD=valvular heart disease; SSS=sick sinus syndrome; ASHD=arteriosclerotic heart disease; HCVD=hypertensive cardiovascular disease; LVH=left ventricular hypertrophy; RBBB=right bundle-branch block; LASH=left anterior superior hemiblock; FRP-AVN=AV nodal functional refractory period; ERP-AVN=AV nodal effective refractory period; FRP-A=atrial functional refractory period; ERP-A=atrial effective refractory period; S=slow pathway; F=fast pathway.

anomalous pathway conduction) during right ventricular pacing, as manifested by appropriate increases in VA conduction times with increasing pacing rates (10 beats/min increments) and also during coupled ventricular stimulation. Group 2 included 4 patients with documented reproducible dual pathway AV nodal re-entrant paroxysmal supraventricular tachycardia (PSVT). These patients fulfilled criteria previously described by our laboratory (Denes *et al.*, 1973). Clinical and electrophysiological data concerning all patients are presented in Table 1.

All patients were studied in the postabsorptive, non-sedated state. Informed consent was obtained in all patients. All drugs were discontinued 48 hours before the study. A tripolar electrode catheter was introduced percutaneously into the right femoral vein and placed across the tricuspid valve to record His bundle and low septal right atrial electrograms (Scherlag *et al.*, 1969). A quadripolar electrode catheter was introduced into the left femoral vein, advanced into the high lateral right atrium, and positioned at the superior vena caval right atrial junction. The two distal pairs of electrodes were used for atrial pacing and the two proximal electrodes to record high right atrial electrograms. A bipolar electrode catheter, introduced via a right antecubital vein, was positioned in the distal coronary sinus to record postero-inferior left atrial electrograms. The position of the catheter in the coronary sinus was confirmed by its posterior location in the lateral view and by the presence of inverted P waves in leads II and III during stimulation. In addition, a 5F bipolar electrode was introduced through the same antecubital vein and positioned at the right ventricular apex for ventricular pacing. Bipolar interelectrode distance for all catheters was 1 cm.

Refractory periods were determined using the extrastimulus technique (Wit *et al.*, 1970). Stimuli were 2 ms in duration and twice diastolic threshold in intensity, and supplied by a digital programmable pulse generator[1]. Intracardiac electrograms, including high right atrium (HRA) and coronary sinus (CS), as well as electrocardiographic standard leads I, II, III, and chest lead V1, were simultaneously displayed on an oscilloscope and recorded on a multichannel photographic recorder[2] at paper speeds of 100 and 200 mm/s.

Electrophysiological definitions

Previous definitions of PA, AH (LSRA-H), and HV intervals, as well as AV nodal functional and effective refractory periods (FRP and ERP) were used (Denes *et al.*, 1974). HRA_1, $LSRA_1$, CS_1, H_1, and V_1 were, respectively, high right atrial, low septal right atrial, coronary sinus, His bundle, and ventricular electrograms of the sinus or driven beats (S_1). HRA_2, $LSRA_2$, CS_2, H_2, and V_2 were electrograms in response to the extrastimulus (S_2).

Procedure

Group 1 patients 1) The antegrade sequence of atrial activation was mapped during sinus rhythm and the following intervals measured: a) P-HRA: from the beginning of the P wave in the electrocardiographic leads to the high right atrial electrogram. b) P-LSRA: from the beginning of the P wave to the low septal right atrial electrogram. c) P-CS: from the beginning of the P wave to the coronary sinus electrogram. d) P-H: from the beginning of the P wave to the His bundle electrogram.

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2) The right atrium (RA) was paced at rates slightly faster than sinus rhythm and then increased in 10 beats/min increments until AV nodal Wenckebach periods resulted.

3) The right ventricle (RV) was paced at rates slightly above the control sinus rate to ensure constant retrograde conduction, and the rate was then increased in 10 beat/min increments until retrograde Wenckebach periods were noted.

4) Ventriculoatrial conduction times (VA) were measured from the ventricular stimulus artefact to the first high frequency potential of the LSRA electrogram. ΔVA time was defined as the difference in VA conduction times obtained by pacing the RV at rates slightly above spontaneous sinus rate and those obtained at a rate slightly slower than that producing retrograde Wenckebach periodicity.

5) The retrograde sequence of atrial activation was mapped during 1:1 right-ventricular pacing and during coupled ventricular pacing at cycle lengths of 600–900 ms. The following intervals were measured: a) S-LSRA: from the stimulus artefact to the first high frequency deflection of the low septal right atrial electrogram. b) S-CS: from the stimulus artefact to the coronary sinus electrogram. c) S-HRA: from the stimulus artefact to the high right atrial electrogram. In two of the patients, in addition to distal coronary sinus, we also mapped the proximal coronary sinus. The latency between the stimulus artefact and the ventricular electrogram was insignificant in all cases. For purposes of analysis, the retrograde atrial activation sequence was measured at a paced ventricular cycle length of 600 ms (100 beats/min) in all patients.

In group 2 patients, in addition to the above procedure, the retrograde sequence of atrial activation was studied during episodes of induced paroxysmal supraventricular tachycardia, and the following intervals were measured: a) V-LSRA: from the onset of ventricular depolarization in the surface electrocardiogram to the first high frequency potential of the low septal right atrial electrogram. This interval could have a negative value in those cases where LSRA preceded the onset of the QRS. b) V—CS: from the onset of ventricular depolarization on the surface electrocardiogram to the onset of ventricular depolarization to the first high frequency potential in the high right atrial electrogram. V-HRA: from the onset of ventricular depolarization to the first high frequency potential in the high right atrial electrogram. All intervals represent the averate of 10 beats.

Results

Antegrade sequence of atrial activation

Individual values, as well as mean values for P-HRA, P-LSRA, P-CS, and P-H for both groups 1 and 2 are presented in Table 2. In every patient, the sequence of antegrade atrial activation was as follows: HRA, LSRA, and then CS.

Retrograde atrial activation sequences

During right ventricular pacing with 1:1 VA conduction, a consistent pattern of retrograde atrial activation was observed in both groups (Fig. 1, Table 3). In all patients except one, the sequence of retrograde atrial activation was as follows: low septal right atrium, coronary sinus, and high right atrium. In the one exception (Case 12), high right atrium slightly preceded coronary sinus. In the 2 patients in whom proximal coronary sinus was also mapped, this followed low septal right atrium by 10

TABLE 2 *Antegrade conduction times during sinus rhythm (ms)*

Case No.	*P-HRA*	*P-LSRA*	*P-CS*	*P-H*	*W (beats/min)*
Group 1					
1	12	38	70	130	110
2	13	45	80	124	150
3	25	42	96	138	120
4	13	34	78	123	180
5	12	35	71	122	220
6	18	43	85	163	150
7	15	42	74	118	190
8	15	59	94	204	120
Mean±SEM	15±2·	42±2·8	81±3·5	140±10·4	155±13·8
Group 2					
9	10	41	57	99	180
10	5	26	89	148	160
11	19	40	98	127	170
12	15	50	80	141	190
Mean±SEM	12±3	39±5	81±8·8	128±11	175±6·4

Abbreviations: See text for definition of P-HRA, P-LSRA, P-CS, and P-H. W=Paced rate producing AV nodal Wenckebach periods.

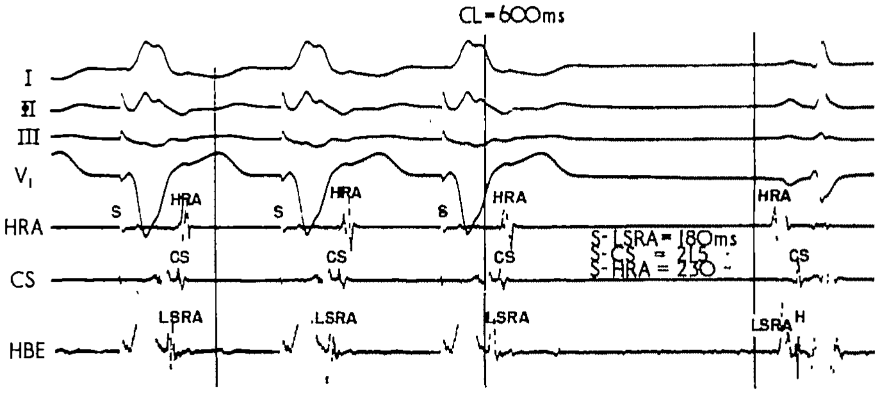

FIG. 1 *Case 4. Retrograde atrial activation sequence during right ventricular pacing at cycle length of 600 ms (100 beats/min). Shown are leads I, II, III, and V1. HRA=high right atrial electrogram; CS=coronary sinus electrogram; LSRA=low septal right atrial electrogram; S=stimulus artefact. In this and subsequent illustrations, paper speed was 100 mm/s, and time lines are at 1 s.*

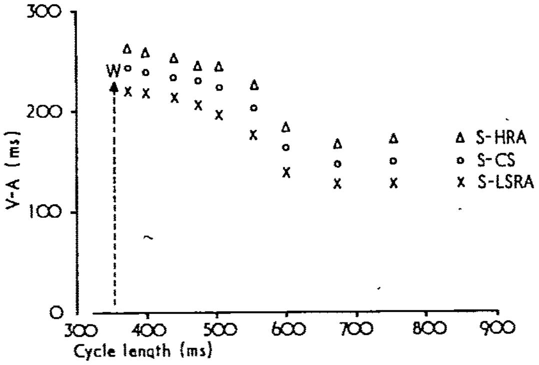

FIG. 2 *Case 6. The retrograde atrial activation sequence during right ventricular pacing at increasing rates is shown. The VA conduction time is represented on the ordinate in ms. The cycle length of ventricular pacing is expressed on the abscissa. Note that the sequence of activation LSRA-CS-HRA does not change with increasing pacing rates.*

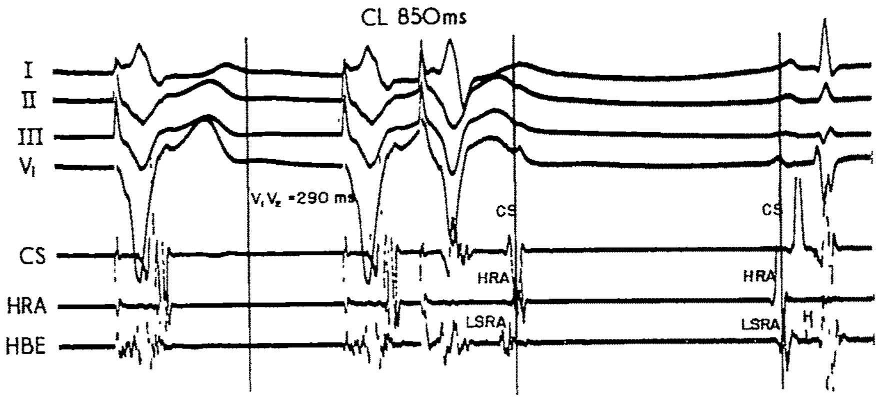

FIG. 3 *Case 6. Coupled right ventricular pacing at cycle length of 850 ms. Note that at V_1V_2 of 290 ms, the retrograde atrial activation sequence is identical to the basic driving rate.*

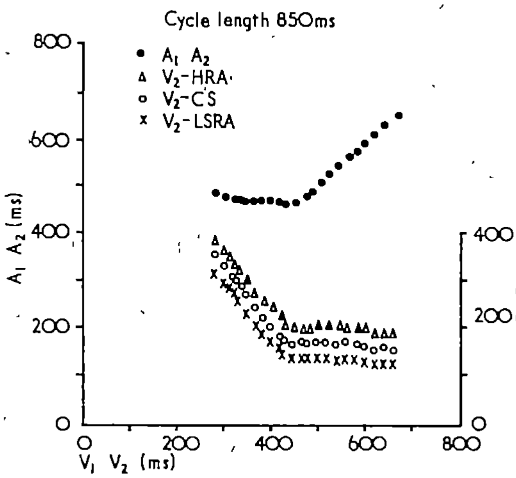

FIG. 4 *Case 6. Coupled right ventricular pacing at cycle length of 850 ms. On the left (ordinate), A_1-A_2 is plotted against V_1V_2. On the right (ordinate), V_2A_2 is plotted against V_1V_2. Note that the retrograde atrial activation sequence remains similar, despite appropriate increases in V_2A_2.*

and 15 ms, and preceded distal coronary sinus by 40 and 30 ms, respectively.

The retrograde atrial activation sequence did not change with ventricular pacing at increasing rates. An example is shown in Fig. 2. VA conduction times were plotted against right ventricular pacing rates (expressed in cycle length). The right ventricle was paced at 70 beats/min, and then in 10 beats/min increments until retrograde Wenckebach resulted at a rate of 170 beats/min. The VA time remained unchanged until 670 ms (rate of 90/min) and then increased progressively up to the point of retrograde Wenckebach. The sequence of retrograde atrial activation remains unaltered at all pacing rates.

The retrograde sequence of atrial activation was also analysed during right ventricular coupled stimulation. Fig. 3 and 4 are representative examples. Activation sequences remained unchanged, despite appropriate increases in V_2-A_2.

Retrograde sequence of atrial activation during paroxysmal supraventricular tachycardia

The low septal right atrium was activated earliest during induced episodes of paroxysmal supraventricular tachycardia in all patients (Fig. 5 and Table 4). In 3 of the 4 patients, coronary sinus electrograms preceded high right atrial electrograms. In one patient (Case 12), the high right atrial electrogram preceded the coronary sinus electrogram by 2 ms.

Discussion

The human heart is frequently capable of retrograde conduction. This ability has been demonstrated during spontaneous junctional (Puech and Grolleau, 1972; Damato and Lau, 1969) and ventricular rhythms (Winternitz and Langendorf, 1944; Kistin and Landowne, 1951; Kistin, 1961), and during electrophysiological studies using ventricular pacing (Damato, Lau, and Bobb, 1970; Goldreyer and Bigger, 1970). The reported frequency of ability for retrograde conduction has varied from 8 to 94 per cent (Samet, Castillo, and Bernstein,

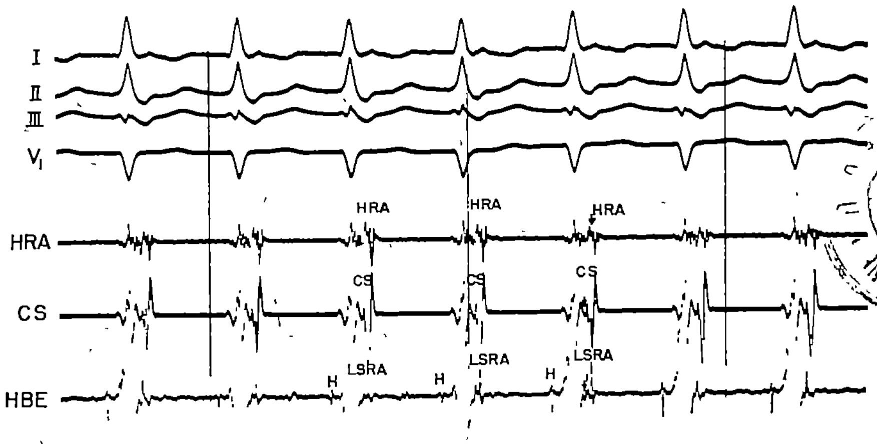

FIG. 5 *Case 10. Retrograde atrial activation sequence during induced AV nodal re-entrant PSVT. Note that low septal right atrium (LSRA) precedes coronary sinus (CS) and high right atrium (HRA).*

TABLE 3 *Retrograde conduction times (in ms) during ventricular pacing at cycle length of 600 ms*

Case No.	*S-LSRA*	*S-CS*	*S-HRA*	*△VA*	*W (beats/min)*
Group 1					
1	100	120	138	20	170
2	135	160	185	25	180
3	155	169	199	30	180
4	180	215	230	20	150
5	175	216	222	20	150
6	140	165	185	90	170
7	230	250	285	25	140
8	220	270	283	25	140
Mean ± SEM	167 ± 15·5	196 ± 17·9	216 ± 17·8	32 ± 8·4	160 ± 6
Group 2					
9	135	155	195	25	190
10	220	232	252	45	150
11	160	172	192	35	150
12	175	203	201	50	170
Mean ± SEM	172·5 ± 18	190·5 ± 17	210 ± 14	39 ± 5·5	165 ± 9·6

Abbreviations: See text for definitions of S-LSRA, S-CS, S-HRA, and △VA. W = paced rate producing retrograde AV nodal Wenckebach periods.

1967; Kistin, 1961; Lister *et al.*, 1967; Narula, 1974; Goldreyer and Bigger, 1970). The sequence of retrograde atrial activation in man has received less attention. Kraus, Yahini, and Neufeld (1966) using indirect pressure recordings from both atria, showed that the left atrium was activated first in one patient with premature ventricular contractions and intact VA conduction. Massumi *et al.* (1969) studied 18 patients with intact VA conduction during right ventricular pacing. In 11 patients, the right atrium was activated an average of 15 ms before the left atrium; in 6 patients, both atria depolarized almost simultaneously, and in one, the left atrium preceded the right atrium. During left ventricular pacing in 2 out of 3 patients, the left atrium was activated first. In their study (Massumi *et al.*, 1969), a bipolar electrode catheter was used to explore the right atrium and an oesophageal bipolar electrode the left atrium. The location of the recording intracardiac electrodes was not precisely delineated. More recently, Svenson *et al.* (1974) reported on one patient without pre-excitation: during RV pacing, the low septal right atrial electrogram preceded low lateral right atrium and lateral left atrium (recorded from the distal coronary sinus). This observation is in agreement with our findings, that in both groups of patients, low septal right atrial activation always preceded distal coronary sinus and high right atrial activation. The demonstration of early activation of the low septal right atrium is consistent with previous experimental observation in animals. Thus, Spach *et al.* (1971), studying the retrograde excitation sequence in isolated hearts of dogs and rabbits, found that initial atrial activation occurred in an area over the posteroinferior region of the AV node, and that from there, the wave front spread over the lower septum. Mignone and Wallace (1966), by mapping the endocardial surface of the right atrium in dogs with a bipolar probe electrode, found that during ventricular pacing with retrograde transmission, the earliest atrial activity was recorded near the ostium of the coronary sinus and approximately 1 cm above the AV ring; 3 to 12 ms later, atrial tissue at the region where a chronically His electrode was implanted was activated (LSRA). In dogs, Damato *et al.* (1970) studied the retrograde atrial mapping during RV or His bundle pacing, and found that the lower portion of the atrial septum was activated first, followed next by Bachman's bundle, the coronary sinus, and then the sinus node.

TABLE 4 *Retrograde atrial activation sequence during PSVT (in ms)*

Case No.	*V-LSRA*	*V-CS*	*V-HRA*
9	−5	45	65
10	70	85	100
11	10	25	50
12	75	98	96
Mean ± SEM	36 ± 20·5	63 ± 17	78 ± 12·1

Abbreviations: See text for definitions of V-LSRA, V-CS, and V-HRA.

Retrograde atrial activation during AV nodal re-entrant PSVT

Current evidence suggests that the underlying mechanism of most paroxysmal supraventricular tachycardia is an intra-AV nodal circus movement caused by functional longitudinal dissociation

(Denes *et al.*, 1973; Wu and Denes, 1975). In most patients with AV nodal re-entrant paroxysmal tachycardia, AV nodal conduction curves (A_1-A_2, H_1-H_2) are discontinuous, suggesting dual AV nodal pathways. The 4 cases included in this study fulfilled the previously described criteria for dual AV nodal pathway re-entrant paroxysmal tachycardia (Denes *et al.*, 1973; Wu *et al.*, 1974).

There is little information concerning the sequence of atrial activation during AV nodal re-entrant paroxysmal supraventricular tachycardia. Experimental animal studies suggest a site of re-entrance in the AN region of the AV node (Janse *et al.*, 1971). One might, thus, expect the atria to be activated in a similar fashion to that occurring during retrograde conduction from the ventricle. In the 4 cases of AV nodal re-entrant paroxysmal tachycardia reported in this series, this was so: in each of the 4 cases, retrograde activation of the atria was identical during both ventricular pacing with retrograde conduction and during induced episodes of paroxysmal tachycardia. It is also noteworthy that these activation sequences were similar to those seen in the 8 patients without paroxysmal supraventricular tachycardia.

Clinical implications

In this study, we have shown the following sequence of retrograde activation during both ventricular pacing and during AV nodal re-entrant paroxysmal supraventricular tachycardia: 1) low septal right atrium, 2) coronary sinus, and 3) high right atrium. The finding of a retrograde activation sequence different from the above suggests the presence of an anomalous connexion between ventricles and atria. For example, early activation of the coronary sinus suggests the presence of a left-sided anomalous pathway. Though low lateral right atrial electrograms were not recorded during this study, it seems reasonable to postulate that early activation of the low lateral right atrium (relative to the low septal right atrium) would reflect the presence of a lateral right-sided extranodal pathway.

In a patient with recurrent paroxysmal supraventricular tachycardia, it seems crucial to record retrograde activation sequences during induced episodes of tachycardia. The presence of an abnormal retrograde activation sequence suggests the participation of a retrogradely conducting anomalous pathway in an AV re-entrant circus movement. In a patient with manifest antegrade pre-excitation, the circus movement would generally be consistent with the electrocardiographically predicted site of anomalous pathway, e.g. early activation of coronary sinus in a patient with type A pre-excitation. The finding of early activation of the atrium contralateral to the predicted site of pre-excitation, e.g. early activation of the coronary sinus in a patient with type B pre-excitation, could suggest the presence of a second anomalous pathway used for retrograde conduction (Spurrell, Krikler, and Sowton, 1974b; Denes *et al.*, 1975). The presence of an abnormal retrograde activation sequence in a patient without manifest antegrade pre-excitation suggests the presence of a concealed (unidirectionally conducting) Kent bundle (Spurrell *et al.*, 1974a; Zipes *et al.*, 1974a).

These considerations seem vital when considering a patient for anomalous pathway ablation, because of recurrent paroxysmal supraventricular tachycardia.

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Effects of pacing site on QRS morphology in Wolff-Parkinson-White syndrome

With special reference to 'pseudo-tachycardia-dependent block in accessory pathway' and 'atrial gap'

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In a patient with a Wolff-Parkinson-White (WPW) syndrome type A mid-right atrial stimulation at a rate of 73/min produced a lesser degree of ventricular pre-excitation than when a slower sinus rhythm was present. This paradoxical effect was not related to tachycardia-dependent block in the accessory pathway because pre-excitation again increased at faster pacing rates. It was partly the result of a (proportionally) greater prolongation of intra-atrial conduction time to the accessory pathway than to the atrioventricular node and partly of a faster atrioventricular nodal conduction time. The latter, in turn, could be attributed either to later-than-normal arrival of excitation at the atrioventricular node, at a time when this structure was more recovered, or to a change in the site or mode of entry into the atrioventricular node.

A gap in the atria was present because at a St1-St2 interval shorter than that at which A2 had been blocked in the accessory pathway conduction was again possible, but with longer A1-A2 intervals. Finally, at similar, short, coupling intervals the impulse penetrated the atrioventricular node from the mid-right atrium but not from the coronary sinus. The unusual findings in this case support a recent assumption that in patients with WPW type A atrial stimulation should be performed from the coronary sinus to minimize the potential sources of error which can be produced by intra-atrial delay.

Although the effects of rate on QRS morphology in the WPW syndrome are well known (Gallagher *et al.*, 1975; Wellens, 1975), the results produced by changing the pacing site have not received much attention. Several authors recognized that conduction time from pacing site to accessory pathway (AP) played an important role (Gallagher *et al.*, 1975; Wellens, 1975; Touboul *et al.*, 1973; Wellens, Schuilenburg, and Durrer, 1971; Zipes, Rothbaum, and DeJoseph, 1974; Denes *et al.*, 1974). When the pacing site was close to the AP the pre-excited area was larger than when the site was far away from the AP. In this report we show that the site of stimulation can also influence QRS morphology in the WPW syndrome by exposing an intra-atrial conduction defect (Wellens *et al.*, 1971; Batsford *et al.*, 1974; Castellanos *et al.*, 1970) and probably by altering the moment of arrival of excitation at the atrioventricular node (Castellanos *et al.*, 1970) or by changing the site and mode of entry in this structure (Batsford *et al.*, 1974; Aranda *et al.*, 1976).

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Case report

A 48-year-old man with the WPW syndrome and repetitive supraventricular tachyarrhythmias was referred to the cardiovascular laboratory for electrophysiological evaluation. His bundle recordings and electrical stimulation were performed after explaining the procedure and obtaining consent (Castellanos *et al.*, 1970; Arenda *et al.*, 1976).

The left-sided panel in Fig. 1 was obtained during

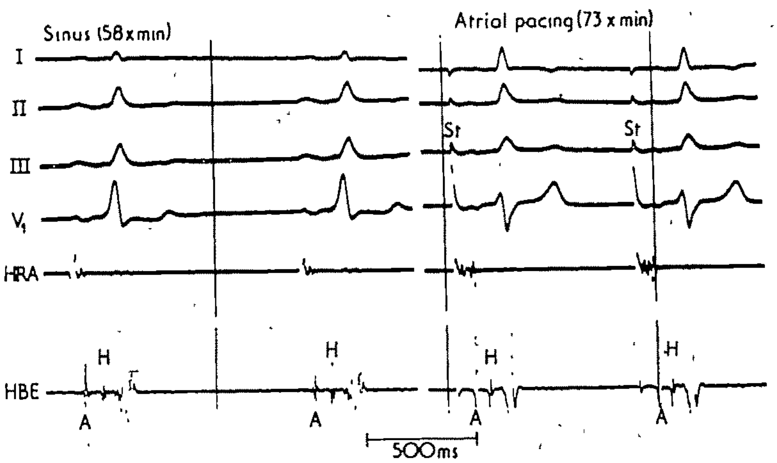

FIG. 1 *Sinus rhythm (rate 58/min) with WPW type A morphology (left). During mid-right atrial stimulation at faster rate (73/min) degree of QRS distortion and bizarreness was less than when sinus rhythm was present. However, ventricular complexes probably still showed some degree of pre-excitation as determined by comparison with QRS morphology resulting from exclusive conduction through normal (atrioventricular node-His-Purkinje) pathway (see end of Fig. 6). Less pre-excitation at faster rates might, at first glance, be attributed to tachycardia-dependent block in the accessory pathway. HRA=high right atrium; HBE=His bundle electrographic lead; A=atrial electrogram recorded in vicinity of atrioventricular node; H=His bundle electrogram; St=pacemaker stimulus artefact.*

sinus rhythm at a rate of 58/min (cycle length 1030 ms). The wide QRS complex showed an initial slurring with a predominantly positive deflection in V1 (WPW type A). The PR and AH intervals measured 125 and 90 ms respectively. The H deflection was inscribed at the onset of ventricular depolarization. Thus the QRS complex was most probably a fusion beat resulting from ventricular activation through both normal (atrioventricular node-His-Purkinje) and accessory atrioventricular pathways. The PA and PH intervals lasted 35 and 125 ms respectively.

Fig. 1, right, was obtained during septal mid-right atrial (MRA) pacing at a rate of 73/min (cycle length 820 ms). The corresponding intervals were of the following duration: St-A, 90 ms; AH, 60 ms; St-H, 150 ms; HV, 40 ms, and St-V, 190 ms. The QRS complexes were narrower and showed a lesser degree of pre-excitation. Though the slightly slurred r wave was smaller than the S wave in lead V1 the r/S ratio in this lead was still greater than in beats resulting from exclusive atrioventricular node-His-Purkinje conduction (end of Fig. 6). This faster rate of decrease in the degree of pre-excitation was unexpected, since it is known that in the WPW syndrome an increase in rate generally produces a greater amount of pre-excitation.

The unusual findings in Fig. 1, right, may be explained by assuming that the impulse traversing the atrioventricular node-His-Purkinje pathway was responsible for activating a greater part of the ventricles than during sinus rhythm. This, in turn, probably reflected the fact that intra-atrial conduction time appeared to have been longer (from the paced site) to the AP than to the atrioventricular node. However, other factors such as a shortening of atrioventricular nodal conduction time (given by a decrease in the AH interval from 90 ms to 60 ms) might have also played a role (see Discussion).

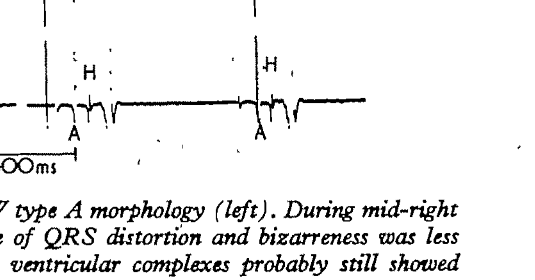

FIG. 2 *During mid-right atrial stimulation at rate of 120/min (left) degree of pre-excitation increased (as compared to when rate was 73/min), indicating that tachycardia-dependent block in accessory pathway was not responsible for decrease in pre-excitation observed in Fig. 1. Right-sided panel shows QRS complexes resulting from exclusive accessory pathway conduction.*

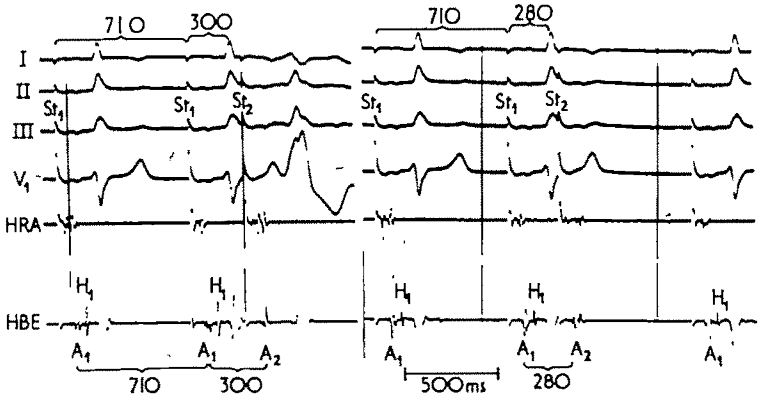

FIG. 3 *Mid-right atrial stimulation at St1-St2 and A1-A2 intervals of 300 ms (left). A2 reached ventricles with QRS morphology attributed to exclusive accessory pathway conduction. At St1-St2 and A1-A2 intervals of 280 ms A2 was blocked in both normal and accessory pathways (right). St1 and St2=driving and testing stimuli, respectively; A1 and H1 and A2 and H2=right atrial and His bundle deflections produced by driving and testing stimuli, respectively. All values in ms.*

At a stimulation rate of 120/min (Fig. 2, left) QRS morphology again resembled that seen during sinus rhythm. This occurred at a cycle length (500 ms), which was almost half that when sinus rhythm was present. The conduction intervals had the following values: St-A, 90 ms; AH, 90 ms; St-H, 180 ms; HV 10 ms, and St-V, 190 ms. Since the St-A and St-V intervals had the same values as those in Fig. 1, right, it was assumed that the intra-atrial conduction time did not increase. The greater degree of pre-excitation compared with when the rate was 73/min may be explained by the *rate-related* increase in atrioventricular nodal conduction time.

The right-sided panel in Fig. 2 shows the morphology that appeared to have resulted from exclusive AP conduction. At a rate of 175/min the H deflection was lost within the ventricular electrogram of the His bundle electrographic lead. The third stimulus artefact (St) produced an atrial deflection which was blocked in both normal and accessory pathways.

Pacing with the extrastimulus method (Wit *et al.*, 1970) from a mid-right atrial site (MRA) was performed at a basic cycle of 710 ms. Driven QRS complexes thus showed a lesser degree of pre-excitation than when sinus rhythm was present. At coupling intervals between 750 and 320 ms the St1-St2, A1-A2, and V1-V2 intervals were similar. When St1-St2 and A1-A2 measured 310 ms and 300 ms (Fig. 3, left), H2 was lost within the

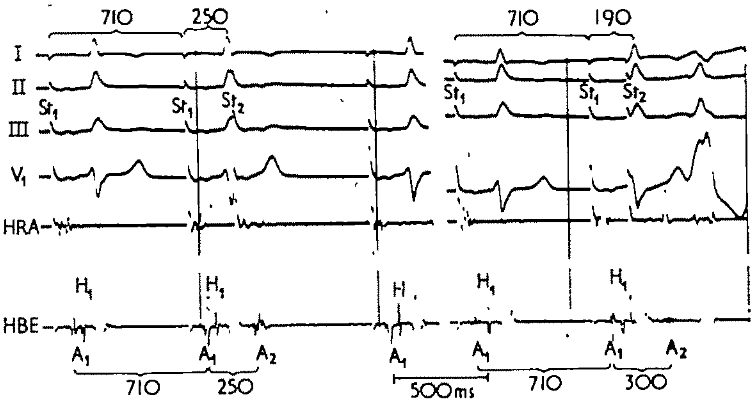

FIG. 4 *At St1-St2 and A1-A2 intervals of 250 ms A2 was blocked in both normal and accessory pathways (left). At St1-St2 interval of 190 ms A1-A2 measured 300 ms. A2 was conducted because it was sufficiently delayed in atria so as to reach accessory pathway after end of its effective refractory period (atrial gap).*

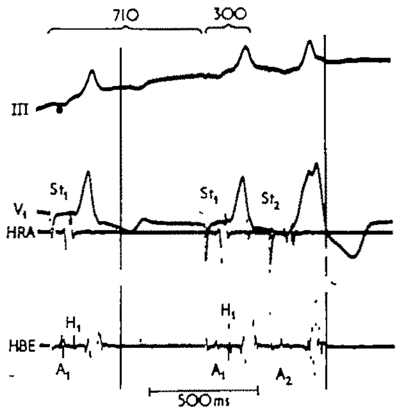

FIG. 5 *Coronary sinus stimulation at same cycle length (710 ms) as that at which mid-right atrium was paced (Fig. 3 and 4) showing greater pre-excitation. Exclusive accessory pathway conduction occurs at St1-St2 and A1-A2 interval of 300 ms.*

ventricular electrogram (V2) recorded by the HBE lead. The QRS morphology corresponded to that attributed to exclusive AP conduction. At St1-St2 and A1-A2 intervals between 280 and 250 ms A2 was not followed by either H2 or V2 (Fig. 3, right, and Fig. 4, left). This occurred because A2 reached the atrioventricular node and AP during their effective refractory period.

At St1-St2 intervals ranging between 230 and 190 ms the A1-A2 intervals again increased to 300 ms. Conduction to the ventricles was therefore possible almost exclusively through the AP with V1-V2 intervals of 320 ms (Fig. 4, right). Since this occurred with St1-St2 intervals shorter than those at which atrioventricular conduction had failed, it seems that there was an atrial gap (Wu *et al.*, 1974) between the paced site and the entrance to the AP. The difference between St1-St2 and A1-A2 intervals (300–190 = 110 ms) suggests that St2 was significantly more delayed in the atria than St1. Finally, the effective refractory period of the atria was reached at a St1-St2 interval of 180 ms.

Pacing with the extrastimulus technique at the same driving cycle length (710 ms) from the coronary sinus (CS) showed that QRS complexes produced by St1 had a greater degree of pre-excitation than when paced from the MRA (Fig. 5). The St-V (100 ms) and St-H (100 ms) intervals were shorter than during MRA driving (Fig. 3 and 4). At St1-St2 intervals from 750 to 290 ms both A1-A2 and V1-V2 intervals were the same (Fig. 5).

However, when the St1-St2 and A1-A2 intervals were reduced to 280 ms (Fig. 6) A2 was blocked in the AP and conducted exclusively through the atrioventricular node-His-Purkinje pathway with a normal (50 ms) HV interval and narrow QRS complex to initiate a run of reciprocating atrioventricular tachycardia. Note that at similar St1-St2 and A1-A2 intervals A2 had been unable to penetrate the atrioventricular node when the MRA was paced (Fig. 3, right). This explains why the tachycardia was elicited only when the CS was paced.

In this patient CS stimulation was not performed with St1-St2 intervals of less than 270 ms because St2 consistently produced long lasting runs of tachycardia.

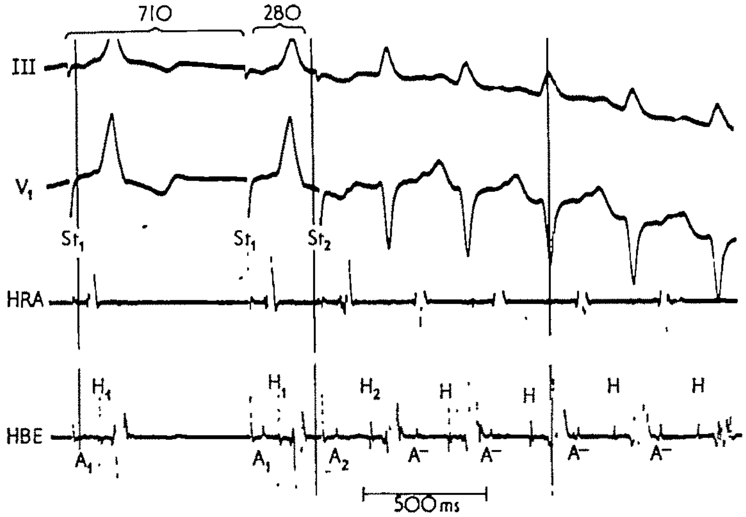

FIG. 6 *Reciprocating atrioventricular tachycardia triggered by premature stimulus delivered to coronary sinus. Arrhythmia occurred at A1-A2 interval (280 ms) at which atrioventricular nodal conduction had not been possible during mid-right atrial pacing (Fig. 3, right). A^-= retrograde atrial deflections.*

Discussion

Several factors are responsible for the different QRS morphologies seen in patients with the WPW syndrome. With the same site of stimulation an *increase in atrial rate* usually produces a greater degree of pre-excitation because the pacing-induced atrioventricular nodal delay decreases the amount of ventricular muscle depolarized by the impulse traversing the normal (atrioventricular node-His-Purkinje) pathway (Castellanos *et al.*, 1970; Wellens *et al.*, 1971; Wellens and Durrer, 1975).

At a *constant* rate changing the pacing site influences QRS morphology because of differences in conduction time between the area of impulse initiation and the atrial end of the AP. Thus in WPW type A CS stimulation results in shorter St-V intervals and wider QRS complexes (Fig. 1) than does right atrial pacing (Fig. 5). The reverse occurs in WPW type B—that is, the St-V intervals and QRS complexes are shorter and wider, respectively, from the right atrium than from the CS (Touboul *et al.*, 1973; Denes *et al.*, 1974). In addition, at a *constant rate* the pacing site may also influence QRS morphology by altering the moment of arrival of excitation at the atrioventricular node (Castellanos *et al.*, 1970) and by changing the site and/or mode of entry into the atrioventricular node (Batsford *et al.*, 1974; Aranda *et al.*, 1976). For example, in a patient with WPW type B reported by Castellanos *et al.* (1970) two different QRS patterns and alternating St-A intervals were seen at a pacing rate of 155/min. Narrow ventricular complexes and (presumably) shorter AH intervals occurred when the St-A intervals had a value of 100 ms compared with when they measured 50 ms. Moreover, Batsford *et al.* noted that in 50 per cent of their patients with normal PR intervals in whom high right atrial and CS pacing were performed atrioventricular nodal conduction and refractoriness appeared to have been faster and shorter, respectively, from the CS than from the high right atrium (Batsford *et al.*, 1974).

In a given case the variations in QRS morphology observed by changing the site and/or rate of pacing are the result of an interplay of factors. For example, the decrease in the amount of pre-excitation during MRA stimulation at a rate of 73/min (as compared with when sinus rhythm was present at a rate of 58/min) did not result from the existence of an accessory pathway with a long effective refractory period (tachycardia-dependent block in the accessory pathway), since the QRS complexes again became wider at even faster rates (Fig. 2)

The unusual response seen in Fig. 1, right, suggests that the impulse traversing the normal pathway contributed more to ventricular depolarization than that propagating through the AP. This could have resulted in part from a proportionally greater increase in intra-atrial conduction time to the accessory pathway than to the atrioventricular node and in part from a faster atrioventricular nodal conduction time. The latter, in turn, might have reflected the pacing-induced, relatively late arrival of excitation at the atrioventricular node at a moment when this structure was more recovered (Castellanos *et al.*, 1970), or a change in the site or mode of entry into the atrioventricular node (Batsford *et al.*, 1974; Aranda *et al.*, 1976).

On the other hand, at faster pacing rates (Fig. 2) the rate-related atrioventricular nodal delay (given mainly by the prolongation of the AH interval) became a more important factor than the intra-atrial conduction time to the AP. Thus the impulse propagating through the atrioventricular node-His-Purkinje pathway contributed less to ventricular depolarization. An atrial gap (Wu *et al.*, 1974) was exposed during MRA pacing with the extrastimulus technique, since the premature stimulus delivered to the atria could activate the ventricles *exclusively* through the AP at shorter coupling intervals than those at which it had been unable to do so (Fig. 3 and 4). This was seen at a St1-St2 interval of 190 ms because the wavefront produced by St2 was sufficiently delayed in the atria by an increase in latency or conduction time, or both. Therefore it reached the AP after the end of its effective refractory period.

This type of gap occurred only between the atria and the AP because conduction was not resumed through the atrioventricular node-His-Purkinje pathway. According to the classical mechanism used to explain the gap phenomena the effective refractory period of the AP must have been longer than the functional refractory period of the atrium (Wu *et al.*, 1974). However, the relatively long time that the impulse had to traverse the atria early in the relative refractory period also favoured the occurrence of the gap.

In the absence of a better measurement it is customary to plot A1-A2 intervals against V1 (delta 1)-V2 (delta 2) intervals when determining the AP's effective refractory period (Castellanos *et al.*, 1973). Yet it should be understood that an atrial electrogram recorded from close to the entrance to the AP may, especially in WPW type A, give more valid results than an electrogram recorded from the right atrium in the vicinity of the atrioventricular node.

Pacing with the extrastimulus technique from the CS showed that at the same driven cycle length as that from the MRA the QRS complex showed greater pre-excitation. Since the AH interval had similar values, this may be considered to be the result of the shorter conduction time between the CS and atrial end of the AP. The shorter time that the impulse had to reach the AP during the relative refractory period also explains why an atrial gap was not seen during CS stimulation.

Another interesting phenomenon was that at short coupling intervals the premature impulse delivered to the CS activated the His bundle through the atrioventricular node at an A1-A2 interval at which from the MRA it had been unable to do (Fig. 3, right, and Fig. 6). Because this was the interval at which reciprocating tachycardias occurred, the arrhythmias were therefore triggered only by CS stimuli. Again, as mentioned previously, differences in the place of impulse initiation may have produced a change in the site and/or mode of entry into the atrioventricular node.

Finally, the findings in this case support a recent statement that CS stimulation is superior to right atrial pacing in the evaluation of patients with WPW type A (Gallagher *et al.*, 1975; Wellens and Durrer, 1975). However, the effects of right atrial stimulation in these cases still require further study.

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Endomyocardial fibrosis
Problems in differential diagnosis

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The clinical and angiographic findings in 5 consecutive patients with congestive cardiac failure are presented to illustrate the pitfalls in the clinical diagnosis of endomyocardial fibrosis. In one patient the clinical diagnosis was confirmed at angiography while another patient who had angiographic evidence of early right ventricular endomyocardial fibrosis was diagnosed clinically as mitral stenosis. In 2 patients the clinical diagnosis was erroneous, there being no evidence of endomyocardial fibrosis on angiography. The fifth patient, who had angiographic evidence of idiopathic cardiomegaly, was diagnosed clinically as either idiopathic cardiomegaly or advanced left ventricular endomyocardial fibrosis. In tropical countries, where endomyocardial fibrosis, rheumatic heart disease, and idiopathic cardiomegaly are common, accurate clinical diagnosis of endomyocardial fibrosis is often difficult and angiographic studies are essential for confirmation.

The clinical, pathological, haemodynamic, and radiological features of endomyocardial fibrosis are well known (Davies, 1948; Ball, Williams, and Davies, 1954; Shillingford and Somers, 1961; Parry and Abrahams, 1963; World Health Organization, 1965; Cockshott, Saric, and Ikeme, 1967; Somers *et al.*, 1968 a, b) but the aetiology is not. While an accurate bedside diagnosis is sometimes possible in advanced right ventricular or biventricular disease (Abrahams, 1962; World Health Organization, 1965; Fowler and Somers, 1968), difficulties may arise in mild to moderate cases where the clinical features of mitral or tricuspid regurgitation may be confused with rheumatic heart disease and idiopathic cardiomegaly (congestive cardiomegaly of obscure origin). We report here the clinical and angiographic findings in 5 consecutive cases of endomyocardial fibrosis to show the difficulties that may frustrate a bedside diagnosis.

Patients and methods

The patients were referred to the cardiac clinic of University College Hospital, Ibadan, in congestive cardiac failure. After physical examination and preliminary investigations cardiac catheterization was done by the usual technique. Pressures were measured by a Statham pressure transducer Model P23 DB and recorded by an Electronics for Medicine Multiple Channel Recorder. A point midway between the plane of the patient's sternum and the plane of the catheter table was taken as the zero pressure baseline. Angiograms were taken with an Elema-Schonander AOT rapid film changer.

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Case reports

Case 1

A boy of 13 years was first seen in June 1974 with a year's history of exertional dyspnoea, cough, and progressive swelling of the face and abdomen. He had had no previous illness. He had bilateral proptosis and was severely dyspnoeic. His jugular veins were engorged and, though the height of the jugular venous pressure could not be assessed accurately, a giant 'v' wave with a steep 'y' descent were discernible. His pulse was of low volume and he had atrial fibrillation with a ventricular rate of about 120/min. His blood pressure was 90/60 mmHg (12·0/8·0 kPa) and there was obvious pulsus paradoxus. No murmur was heard but an early 3rd sound was audible at the apex and also at the left sternal edge. His pulmonary closure sound (P2) was not loud. He had bilateral rhonchi but no crepitations in the chest. His liver was enlarged to 5 cm below the ribs and showed systolic pulsation. Gross ascites was present though he had only minimal ankle oedema.

A diagnosis of right ventricular endomyocardial fibrosis with pericardial effusion was made. An electrocardiogram showed low voltage QRS complexes, atrial fibrillation, and right ventricular preponderance. Chest *x*-ray examination showed oligaemic lung fields and an enormously enlarged heart, with a silhouette indicating pericardial effusion. Laboratory investigations were normal except for an eosinophilia of 13 per cent out of a total white count of $7400/\text{mm}^3$ and a low serum albumin of (2·3 g/100 ml).

Two pericardial taps were performed at different times during his stay in hospital and a total of 1100 ml of straw-coloured fluid was removed from the pericardial cavity. Management consisted of bed rest, digoxin, and diuretics. When his condition improved, right heart catheterization was performed and his intracardiac pressures are summarized in the Table. The ventricular tracings showed the typical 'dip-and-plateau' configuration. Angiocardiography showed an enormously enlarged right atrium and severe tricuspid regurgitation. The right ventricle was diminutive in size and had a dilated contractile outflow tract (Fig. 1A and B).

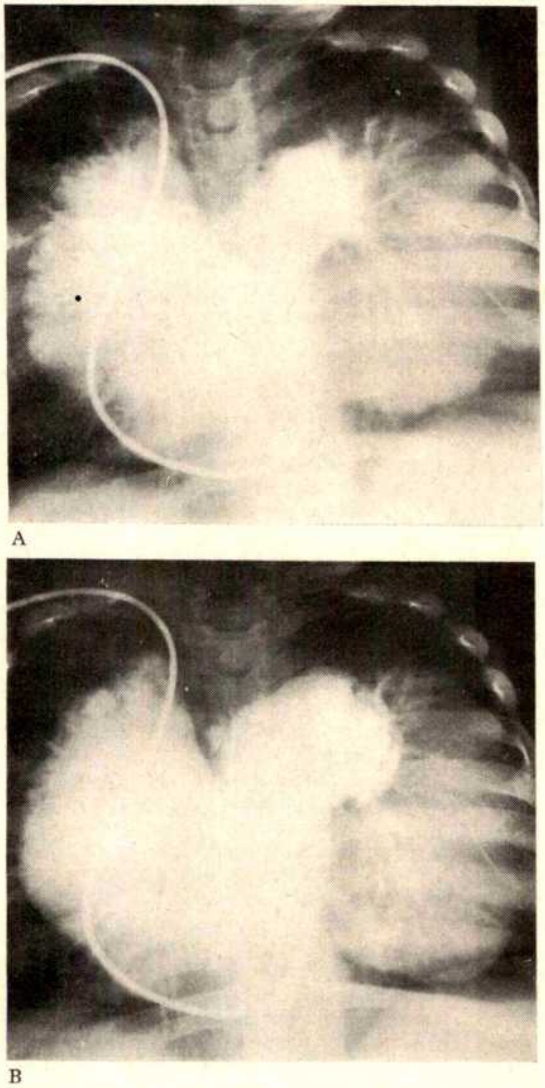

FIG. 1A and B. *Case 1. Right ventricular angiogram, (A) during systole and (B) diastole, showing small right ventricular chamber with dilated contractile outflow portion and gross reflux into aneurysmal right atrium.*

At the time of discharge from hospital he had no ascites or peripheral oedema. His jugular venous pressure was still raised with a prominent 'v' wave.

Case 2

A 20-year-old student was initially admitted to the hospital with congestive cardiac failure in 1973. He had previously been well. He had a right inguinal herniorrhaphy in 1971, when no cardiac disease was found. He was in atrial fibrillation, his pulse was of low volume, and his jugular venous pressure was raised, with a giant 'v' wave. An opening snap followed by a mid-diastolic murmur was heard between the apex and the left sternal edge. The murmur was not constant, it tended to vary, but became easily heard when he was not in heart failure. He also had minimal bilateral ankle oedema, an enlarged pulsatile liver, but no ascites.

He improved considerably on bed rest, digoxin, and diuretics, and was discharged for follow-up as an outpatient. In November 1974 he was readmitted in congestive cardiac failure, but his physical signs had not changed significantly. His electrocardiogram showed atrial fibrillation and inverted T waves in leads II, III, aVF, V1, V2, V3, and V4. There was counterclockwise rotation over the precordial leads. Chest *x*-ray examination showed an enlarged heart with a prominent pulmonary conus. All other laboratory investigations were normal and he had no eosinophilia. A diagnosis of severe mitral stenosis with pulmonary hypertension and functional tricuspid regurgitation was made.

At cardiac catheterization the right ventricle was difficult to catheterize and the pulmonary artery was entered with much difficulty. The patient's intracardiac pressure readings are summarized in the Table. The right ventricular trace showed the typical 'square-root' configuration. The right ventricular angiogram (Fig. 2) showed moderate tricuspid regurgitation with a dilated right atrium. The outflow tract of the right ventricle was dilated and the ventricle itself was shrunken in its main portion. The left ventricular angiogram was normal and there was no evidence of aortic regurgitation on aortic root injection. There was no gradient across the mitral and tricuspid valves. A diagnosis of right ventricular endomyocardial fibrosis was therefore made.

Case 3

A 17-year-old boy was admitted in November 1974 with a three months' history of increasing exertional dyspnoea and swelling of the legs and abdomen. There was no preceding illness. He was in severe congestive failure, his fingers were clubbed, and he was mildly cyanosed. His pulse was of low volume, his blood pressure was 100/60 mmHg (13·3/8·0 kPa), and he was in atrial fibrillation with a pulse rate of about 100/min. The apex beat was displaced but quiet and his jugular venous pressure was raised to the angle of the jaw, with a

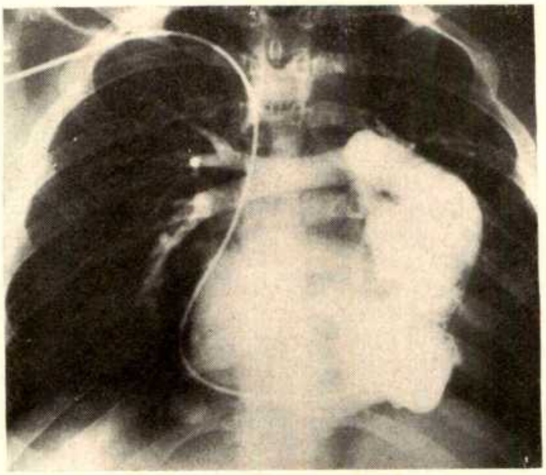

FIG. 2 *Case 2. Right ventricular angiogram showing tricuspid regurgitation, dilated outflow tract, and shrunken right ventricular chamber. Right atrium is also dilated.*

prominent 'v' wave. He had a pansystolic murmur radiating to the axilla together with a loud early third sound. No murmur of tricuspid regurgitation was heard. His chest was clear clinically and his liver was enlarged and pulsatile. An electrocardiogram showed low voltage QRS complexes and atrial fibrillation. Chest *x*-ray examination showed cardiac enlargement which was predominantly right sided but with left atrial enlargement on the lateral film done with barium swallow. The lung fields were clear. A blood film did not show eosinophilia.

A clinical diagnosis of biventricular endomyocardial fibrosis with mitral and tricuspid regurgitation was made. The patient's intracardiac pressures are summarized in the Table. The right ventricular angiogram showed severe tricuspid regurgitation, a dilated right atrium, and a normal-sized right ventricle. A left ventricular angiogram showed a slightly enlarged left ventricle which contracted well. There was, however, severe mitral regurgitation and a small apical aneurysm (Fig. 3). There was no evidence of endomyocardial fibrosis on angiography. The findings suggested primary lesions of the mitral and tricuspid valves.

Case 4

A 45-year-old housewife was admitted with a year's history of exertional dyspnoea and cough. At about the same time she noticed that her abdomen and her ankles were progressively swelling and that she had a pulsation at the side of her neck. She was in severe congestive cardiac failure, her pulse was 80/min, regular, but of low volume. Her blood pressure was 95/65 mmHg (12·6/8·6 kPa). Her apex beat was in the 6th intercostal space at the anterior axillary line and was quiet. There was, however, a right ventricular heave. She had a pansystolic murmur at the apex, louder in expiration and radiating to the axilla. Another pansystolic murmur, louder in inspiration, was heard at the lower left sternal edge. A loud, early third sound was audible at the apex and the P2 was loud. Her chest was clear but she had an enlarged liver with a systolic pulsation. There was no ankle oedema but she had ascites. An electrocardiogram showed sinus rhythm, left atrial enlargement left axis deviation, and T wave inversion in leads V4 to V6 but no left ventricular hypertrophy. Chest *x*-ray examination showed a grossly enlarged heart. Left atrial enlargement was confirmed on the lateral chest film with barium in the oesophagus. Other laboratory investigations were normal except for an eosinophilia of 10 per cent out of a total white blood cell count of 7400.

Biventricular endomyocardial fibrosis was thought to be the most probable diagnosis. The intracardiac pressures at catheterization are summarized in the Table. The right and the left ventricular pressure tracings showed the 'dip-and-plateau' configuration, but no evidence of endomyocardial fibrosis was found at angiography. There was gross mitral and tricuspid regurgitation and all the chambers of the heart were dilated. The left ventricle showed very poor contraction.

Case 5

A 35-year-old housewife was admitted with a 9-months' history of exertional dyspnoea and progressive swelling

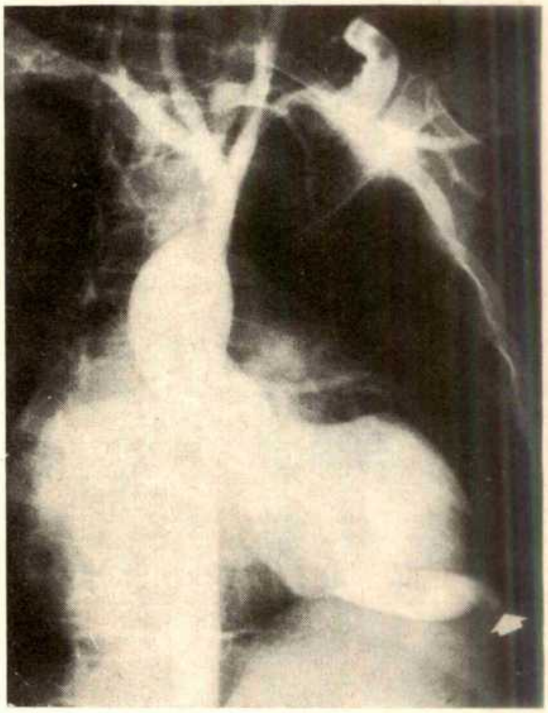

FIG. 3 *Case 3. Left ventricular angiogram during diastole showing slightly dilated left ventricle with severe mitral regurgitation. Ventricle contracted well during systole. Note small aneurysm (see arrow) at apex of heart.*

of the abdomen and feet. The patient also complained of swelling of the face which usually receded as the day advanced. She was in severe congestive cardiac failure with the jugular venous pressure raised to the angle of the jaw, a blood pressure of 90/60 mmHg (12·0/8·0 kPa), massive ascites, sacral oedema, and gross oedema of both legs. Her extremities were cold and her pulse rate was 120/min, regular, but of very poor volume. The apex beat could not be located but there was a right ventricular heave. On auscultation she had no murmurs but a loud third sound was heard at the fifth left intercostal space. Her P2 was loud, there were crepitations at both lung bases, and the liver was enlarged and tender. An electrocardiogram showed left atrial enlargement and T wave inversions in leads II, III, aVF, V1 to V6. Chest *x*-ray examination showed a grossly enlarged heart and a right pleural effusion. She had an eosinophilia of 7 per cent out of a total white count of 5500/mm^3. All other laboratory investigations were normal.

She was thought to be suffering from advanced left ventricular endomyocardial fibrosis though idiopathic cardiomegaly could not be excluded. A left heart study showed a low systolic left ventricular pressure with raised end-diastolic pressure (Table). An angiogram showed a poorly contractile ventricle with severe mitral regurgitation. There was no evidence of endomyocardial fibrosis.

Discussion

The clinical presentation of endomyocardial fibrosis depends on the chamber involved and the severity of the disease. Disease of both ventricles, with mitral and tricuspid regurgitation, occurs more often than disease of only one ventricle (Somers and Fowler, 1968). Right-sided endomyocardial fibrosis presents with three obvious features: a very high venous pressure with a dominant systolic wave indicative of tricuspid regurgitation, massive ascites, and minimal or no ankle oedema (Abrahams, 1962). Left-sided endomyocardial fibrosis presents with mitral regurgitation and features of left ventricular failure. Pulmonary oedema occurs in the early stages, and then later, as the pulmonary vascular resistance rises, signs of pulmonary hypertension are found (Somers and Fowler 1968).

The major effect of endomyocardial fibrosis of either ventricle is to restrict the filling and output of the ventricle (Somers and Fowler, 1968). The haemodynamic effect of this restriction is, however, seen only in advanced cases. Cardiac failure supervenes ultimately, often in the absence of striking cardiac enlargement and with trivial or no murmurs (Somers and Fowler, 1968). In advanced cases the disease may present with severe heart failure without any murmurs but with a loud third heart sound. The latter presentation is seen commonly in right ventricular endomyocardial fibrosis (Abrahams, 1962) and is illustrated by Case 1. Case 2, by contrast, had less severe disease. The finding of a mid-diastolic murmur thought to be the result of mitral stenosis in this patient was misleading and was most probably a flow murmur across the tricuspid valve. This case is similar to that described by Faruque (1963) in a report on endomyocardial fibrosis in adults in Britain. The patient had murmurs suggestive of mitral stenosis but at necropsy was found to have severe biventricular endomyocardial fibrosis.

Cases 3 and 4 show that the clinical picture of biventricular endomyocardial fibrosis may be mimicked by other causes of mitral and tricuspid regurgitation. The angiographic pictures of Case 3 suggested primary diseases of the mitral and the tricuspid valves. Though a type 3 endomyocardial fibrosis affecting only the valvular region (Shaper, Hutt, and Coles, 1968) may produce this picture, rheumatic mitral and tricuspid regurgitation has to be excluded. Finger clubbing and cyanosis further confused the clinical picture as these signs are not uncommon in endomyocardial fibrosis (Abrahams, 1962; Somers *et al.*, 1968b). Though Case 3 was afebrile throughout admission, subsequent blood cultures persistently yielded *Staphylococcus albus* and he was treated for infective endocarditis.

Cases 4 and 5 highlight the difficulty in dis-

TABLE *Intracardiac pressures (mmHg) recorded in all 5 patients*

Case No.	*Right atrium*	*Right ventricle*	*Pulm. artery*	*Pulm. capill. wedge*	*Left ventricle*	*Aorta*
1	v 16	30/14	34/24 Mean 28	—	120/10	—
2	v 18 Mean 14	20/14	20/16 Mean 18	11	120/10	110/60
3	v 20 Mean 16	40/16	40/23	28	140/32	135/82
4	v 14 Mean 10	40/16	40/25	45	120/50	125/80
5	—	—	—	—	95/30	100/65

Conversion factor from Traditional to SI units: 1 mmHg≈0·133 kPa.

tinguishing endomyocardial fibrosis from idiopathic cardiomegaly, also commonly seen in the tropics. Their clinical signs are frequently similar, no age group is exempt from either disease (Ball *et al.*, 1954; Cockshott *et al.*, 1967; World Health Organization, 1965; Antia, 1968), and the finding of a third sound is common to both diseases and is not a very helpful discriminatory sign. The absence of a murmur of mitral or tricuspid regurgitation can occur in advanced stages of both diseases and is the result of poor myocardial function which is not forceful enough to generate audible vibrations.

Cardiomegaly on chest *x*-ray examination is not specific to endomyocardial fibrosis nor is the presence of a large cardiac contour on plain film suggestive of a pericardial collection pathognomonic. Tuberculous pericarditis is prevalent in many areas where endomyocardial fibrosis occurs and both diseases may present as pericardial effusion (Abrahams, 1962). Calcification in the apical endocardium is a very useful diagnostic sign but calcified ventricular aneurysm, common in Nigeria, must be considered as a differential diagnosis (Ive *et al.*, 1967).

The electrocardiogram in endomyocardial fibrosis has no specific diagnostic pattern (Williams and Somers, 1960) and is not very useful at the bedside. The electrocardiographic finding of right ventricular hypertrophy in Case 1 is difficult to explain since the right ventricle was almost non-existent on angiography.

The 'dip-and-plateau' configuration on ventricular trace, which has been used by some as the sole criterion for diagnosis during cardiac catheterization (Ive *et al.*, 1967), is not confined only to patients with endomyocardial fibrosis. It has been reported in amyloidosis (Hetzel, Wood, and Burchell, 1953; Gunnar *et al.*, 1955), in diffuse myocardial fibrosis (Burwell and Robin, 1954), and in cardiomyopathy (Goodwin *et al.*, 1961). It was first reported by Bloomfield *et al.* (1946) in patients with either right ventricular failure with tricuspid regurgitation or constrictive pericarditis, and is evidently a nonspecific pattern of little use for diagnostic purposes.

Right ventricular endomyocardial fibrosis also has to be distinguished from constrictive pericarditis. The venous pressures in both diseases are high, and ascites with minimal or no peripheral oedema is common. Auscultation may give similar findings and the electrocardiograms may be similar (Abrahams, 1962; World Health Organization, 1965). The presence of murmurs may, however, suggest the diagnosis of endomyocardial fibrosis, and obvious pericardial calcification confirms the diagnosis of constrictive pericarditis. Left ventricular endomyocardial fibrosis also has to be distinguished from other causes of mitral regurgitation.

Angiographic study is the most useful procedure in diagnosing endomyocardial fibrosis and it can differentiate rheumatic mitral regurgitation from left ventricular endomyocardial fibrosis (Cockshott, 1965; Cockshott *et al.*, 1967). The angiographic appearances of right ventricular endomyocardial fibrosis are also pathognomonic and easily distinguished from other causes of tricuspid regurgitation and constrictive pericarditis—as Cases 3 and 4 show. Selective angiocardiography, however, is not infallible, since it is useful only when the disease is sufficiently advanced to cause visible deformity in one or both ventricles (Somers and Fowler, 1968).

The diagnosis of endomyocardial fibrosis is therefore fraught with many pitfalls, and angiographic studies are needed in most cases to make a definite diagnosis. Without them investigations may yield misleading results. Definite diagnosis at the present seems to depend upon sophisticated investigations not available in every centre.

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Coarctation of the aorta in infancy and childhood

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The management and results of treatment in 181 children with coarctation of the aorta are presented. In this series, 79 per cent of the patients presented in the first year of life and 55 per cent presented as neonates. One hundred and fifty patients were operated on, with a total surgical mortality of 21 per cent. Only one surgical death occurred in those operated on after 3 months of age. The higher mortality in young infants is closely related to associated cardiac anomalies and to the frequency of aortic and isthmal hypoplasia. Our findings suggest that neonates presenting with heart failure and coarctation should be operated on early, as the surgical mortality under 6 weeks is 45 per cent, whereas there is an 86 per cent mortality in neonates who were not operated on. Analysis of follow-up indicates that when operation can be performed electively the optimal period for surgical treatment is between 6 months and 1 year of age. If operation is performed after this age, there may be persistent systemic hypertension despite relief of aortic obstruction.

Coarctation of the aorta is one of the commonest congenital cardiovascular anomalies in infancy and childhood (Keith, Rowe, and Vlad, 1967). It is a common cause of early heart failure (Rowe and Mehrizi, 1968) and was the fifth most frequent cardiac anomaly in one series of 500 infants undergoing cardiac surgery in the first year of life (Cooley and Hallman, 1964). However, the optimal time for operation is by no means established. When congestive heart failure is a complicating factor during infancy it can be argued that immediate relief of the obstruction is a necessity. In the absence of heart failure the decision regarding timing of surgery is more difficult, since resection in infancy poses considerable technical problems, and it is known that some patients may develop recurrent coarctation. In order to provide data pertinent to this problem we have reviewed the results of management of 181 infants and children with coarctation seen at the Brompton Hospital in the 7-year period between January 1967 and December 1973.

Patients studied

Altogether 181 patients were studied in whom the diagnosis of coarctation of the aorta had been confirmed by either cardiac catheterization and angiocardiography, surgery, or necropsy Their ages ranged from 1 day to 14 years, with a male:female ratio in the whole series of 1·7:1. When coarctation was considered as an isolated condition this ratio was 2·6:1. In contrast, coarctation with associated cardiac anomalies gave a male:female ratio of 1·1:1.

During this period two patients have been seen in whom coarctation was associated with right aortic arch; these have been reported separately (Honey *et al.*, 1975) and are not included in this series.

Clinical presentation

The mode of presentation in four age groups is shown in Table 1.

Associated anomalies

Associated cardiac anomalies, which profoundly influence mode of presentation, were commoner in the younger infants (Table 2). Thus 84 per cent of patients under 1 week and 86 per cent of patients up to 4 weeks had major cardiac anomalies in contrast to 52 per cent of patients between 4 weeks and 1 year of age and 27 per cent of patients over 1 year. It should also be noted that the patients presenting as neonates had more complex anomalies, either cyanotic or acyanotic, than those presenting after this time.

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TABLE 1 *Mode of presentation of coarctation of aorta*

	<1 wk	*1 wk–4 wk*	*4 wk–1 yr*	*1-14 yr*
Total number	55	44	44	38
Heart failure	35	30	18	1
Cyanosis+heart failure	11	7	2	0
Cyanosis	4	0	0	0
Swollen feet	1	0	0	0
Failure to thrive	0	1	2	0
Asymptomatic	4	6	22	37

Diagnosis

Clinical recognition of coarctation depended upon the finding of absent or decreased femoral pulses in all cases. A difference in systolic blood pressure measurements between upper and lower limbs of greater than 30 mmHg (4·0 kPa) was taken as confirmatory evidence of the diagnosis. Over the past two years blood pressure measurements have been recorded using a Doppler shift technique which has been shown to give accurate and reproducible results (Elseed, Shinebourne and Joseph, 1973). Pressure differences of up to 30 mmHg (4·0 kPa) between the upper and lower limbs are commonly found in the normal neonate (de Swiet, Peto, and Shinebourne, 1974), and hence have been disregarded. In the majority of instances cardiac catheterization and angiography were performed. In broad terms the angiographic appearances showed the obstruction to be either a discrete juxtaductal coarctation or more widespread aortic and isthmal hypoplasia (Rudolph, Heymann, and Spitznas, 1972; Shinebourne and Elseed, 1974; Elseed, Shinebourne, and Paneth, 1974). While it is realized that these different types are probably distinct pathophysiological entities, for the purposes of this presentation they have been grouped together as 'coarctation'.

Management

All patients who were admitted to hospital in heart failure were treated with appropriate therapy and in the majority cardiac catheterization was undertaken.

Thirty-five of the 55 neonates presenting in the first week of life had resection of coarctation within the first 6 weeks of life and 12 died before operation could be performed. Five patients had delayed operations, one being performed at 2 months, one at 9 months, and three after 1 year. Three patients had no operation because the gradient between brachial and femoral systolic pressures was small, barely exceeding that found in the normal neonate (de Swiet *et al.*, 1974). Operations were performed on 38 of 44 neonates presenting between 1 week and 4 weeks of age, 25 before 6 weeks, 10 before a year, and 3 after this time. Six patients in this group died before operation could be carried out. Of the 44 infants who were seen between 4 weeks and 1 year, 21 were operated upon before and 17 after 1 year; 6 patients were not operated upon because of minor coarctation. In the 38 children who were older than 1 year at presentation, 24 were operated upon within 1 year of referral and 10 in the subsequent years; the age at operation ranged from 2 to 16 years. Four patients were not operated upon as the coarctation was mild. Fig. 1 relates surgical mortality to age at the time of operation.

Complications of surgery

Operations were performed on 150 (82%) of the 181 patients. Of these, 27 (18%) died within 48 hours of

TABLE 2 *Associated cardiac anomalies in 181 patients with coarctation of aorta*

Associated cardiac anomalies	*<1 wk*	*1 wk–4 wk*	*4 wk–1 yr*	*1–14 yr*
Nil	9	8	21	30 (1)
±PDA±VSD±ASD	22 (8)	21 (4)	9 (2)	4
Atrioventricular canal±PDA	3 (1)	2 (1)		
Total anomalous pulmonary venous drainage±VSD	2 (1)	1 (1)		
Mitral stenosis/regurgitation±PDA	1	3	6	3
Aortic stenosis/regurgitation	1	1	2	
Endocardial fibroelastosis		1	4 (1)	
l-transposition of great vessels±VSD		2 (1)		
d-transposition of great vessels±PDA±VSD	9 (3)	2 (2)	1	
Primitive ventricle±PDA	6 (3)	1 (1)		
Double outlet right ventricle			1 (1)	
Hypoplastic left heart	2 (1)			
Pulmonary hypertension		1		1
Total	55 (17)	44 (10)	44 (4)	38 (1)

Note: Figures in parentheses indicate all operative and postoperative deaths. PDA, persistent ductus arteriosus; VSD, ventricular septal defect; ASD, atrial septal defect.

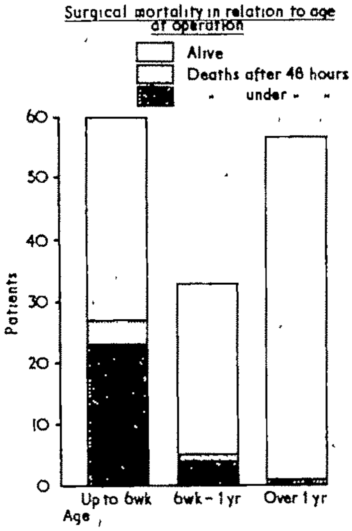

FIG. 1 *Surgical mortality according to age at operation. Note that of deaths under 48 hours in group between 6 weeks and 1 year, only one patient died over age of 3 months.*

operation. There were five deaths after 48 hours. Of these, one could be attributed to the presence of associated endocardial fibroelastosis, one to uncontrollable heart failure and jaundice with suspected septicaemia; one infant died 3 days after operation as a result of severe preoperative acidosis, and in the remaining two cases, death occurred two weeks after operation from unknown causes. Thus, the overall surgical mortality was 21 per cent. Analysis within the age-groups at surgery indicated that the majority who died were under 6 weeks of age (27 of the 32 who died) (Fig. 1). A high proportion of these patients had serious associated cardiac anomalies (Table 2). Between 6 weeks and 1 year of age (33 patients operated) there were four operative and postoperative deaths (12%). After 1 year of age (57 patients operated) only one patient died after operation, a girl whose aorta ruptured in the immediate postoperative period.

Thirty-one patients with proven coarctation did not undergo operation. Of 15 under 1 week, 12 died, and of these nine had severe associated cardiac anomalies. Birth injury, hypothermia, or profound acidosis on admission contributed to death, but seven patients died while the accompanying heart failure was being treated medically. Six patients presenting between 1 and 4 weeks died before operation could be performed, five of these having associated anomalies. The mortality in patients presenting as neonates in whom no operation was performed was therefore 86 per cent. Of the 38 patients who, in the first year of life, were found to have isolated coarctation, 12 presented in heart failure, 10 had immediate operations, with only one death. Our present policy, therefore, is to operate upon all patients with heart failure accompanying coarctation. All the patients presenting above the age of 1 month who were not operated on had coarctation of minor degree and all survived.

Postoperative results of surgery

Patients' data were included only if they were followed for a period of at least 6 months. Eighty-seven patients satisfied this criterion, and of these 24 had their coarctations resected in the first 6 weeks of life and 22 in the period between 6 weeks and 1 year of age. The follow-up periods after operation in the first year were up to 5 years (Fig. 2), with a mean of 2·2 years. The 41 patients operated upon after 1 year had a follow-up period ranging from 6 months to 10 years (Fig. 3), with a mean of 2·7 years. Many of our patients had been referred from other countries, or other centres, thus accounting for the proportionately small number of patients with long-term follow-up data.

In Fig. 2 and 3 upper limb blood pressure at the last follow-up has been compared with the normal

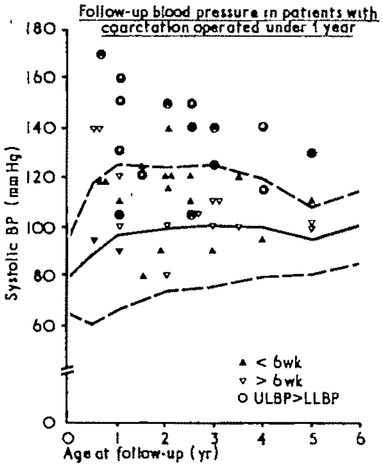

FIG. 2 *Follow-up systolic blood pressure in patients with coarctation operated upon under 1 year of age.* ▲ *<6 weeks;* ▽ *>6 weeks;* O *upper limb systolic blood pressure > lower limb systolic blood pressure. Normal systolic blood pressure (mean±2 SD) is shown by continuous and dashed lines (Master* et al.*, 1950; Nadas and Fyler, 1972). Of 14 patients whose follow-up blood pressure was abnormally high, 10 had diminished femoral pulses.* 1*mmHg* ≈ 0·133*kPa.*

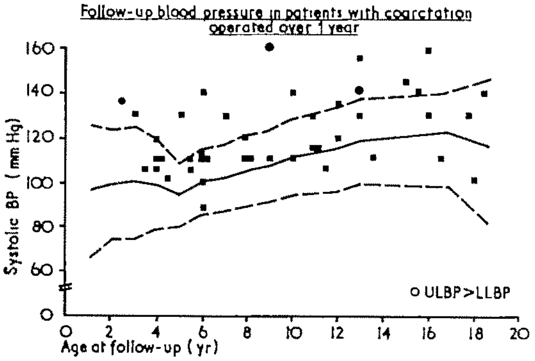

FIG. 3 *Follow-up systolic blood pressure in patients with coarctation operated upon over the age of 1 year.* O *upper limb systolic blood pressure > lower limb systolic blood pressure. Thirteen patients are seen to have abnormally high systolic pressures but in only 2 were femoral pulses diminished.* 1*mmHg* ≈ 0·133*kPa*.

blood pressure for age (Master, Dublin, and Marks, 1950; Nadas and Fyler, 1972). Where there was a discrepancy between the upper and lower limb blood pressure, either by direct measurement or by palpation, this has been indicated on the figures. Of the 24 patients operated on before 6 weeks of age, 29 per cent had a blood pressure above the normal range (7 patients); of the 22 patients operated upon between 6 weeks and 1 year, the corresponding figure was 32 per cent (7 patients). Thirteen of the 41 patients (32%) operated upon when over 1 year of age had a raised follow-up blood pressure. When the data were analysed further, it was found that the majority (10 to 14) of infants operated upon under a year had upper limb hypertension associated with diminished femoral pulses. In contrast, of the 13 patients operated after 1 year, only two of those with upper limb hypertension had diminished femoral pulses (or decreased lower limb blood pressures). Thus, 11 of 13 patients whose upper limb blood pressures were greater than 2 standard deviations above the mean had normal femoral pulses. In those where lower limb blood pressure was measured (by the Doppler technique), a raised lower limb pressure was found.

Thus far, six patients have required reoperation, five having had their first resection performed during the first 6 weeks of life. The remaining patient had her first resection at 6 years of age. The age at reoperation ranged from 3 weeks to 9 years, and there was no mortality.

Discussion

We have presented an analysis of the results of treatment of 181 infants and children referred to our hospital with isthmal hypoplasia or discrete coarctation of the aorta. Our data indicate that a high proportion of neonates and young infants presented in heart failure, making immediate surgery essential. Our earlier experience showed that if operation were not performed in the presence of heart failure, then death was inevitable. Many of the patients presenting in infancy had the isthmal narrowing variety of coarctation. It is now well established that this anomaly reflects reduced aortic flow during intrauterine development (Rudolph *et al.*, 1972; Shinebourne and Elseed, 1974; Elseed *et al.*, 1974): this fact itself usually indicates the presence of additional intracardiac anomalies. Taking into account, therefore, that coarctation is only part of the overall anomaly, the surgical mortalities of 45 per cent below the age of 6 weeks and 12 per cent for patients operated on between 6 weeks and 1 year are not discouraging. The overall mortality in infancy of 31 per cent compares favourably with previous reports, which cite mortalities in infancy from 21 to 56 per cent (Mortensen *et al.*, 1959; Glass, Mustard, and Keith, 1960; Hallman *et al.*, 1967; Tawes *et al.*, 1969; Sinha *et al.*, 1969). We were able to judge the efficacy of the operation in 24 of the 60 patients who had their operation in the first 6 weeks of life and who were followed up for at least 6 months. We found that 30 per cent of these patients had residual hypertension. The feature of the data from this group was that upper limb pressures were increased while lower limb pressures were decreased. This suggests that the hypertension resulted from incomplete removal of the hypoplastic aortic segment, and it is significant that five of the six patients requiring reoperation were in this age group. It may also be relevant that further analysis showed that of the 14 patients with pressure differentials after operation, 13 had been severely ill at the time of operation and a rapid operative procedure had been essential. These findings agree with those of Rathi and Keith (1964), who reported 150 children of whom 27 had their coarctation resected in infancy; they too found 30 per cent in this group with upper limb hypertension and reduced lower limb pressures.

When we critically analyse those of our patients referred as infants, that is between the ages of 1 month and 1 year, we find that only 18 of 44 presented with heart failure. This lower proportion compared with neonates undoubtedly reflects a smaller number of patients with aortic isthmal hypoplasia secondary to intracardiac anomalies. As would be expected in a group of patients with larger hearts and requiring less complicated operations, the operative mortality was also considerably reduced (12%) when operations were performed between 6 weeks and 1 year of age. Furthermore these operative deaths all occurred in patients below the age of 3 months. Twenty-two of the patients were followed up postoperatively and seven had residual hypertension. As with the neonatal group, the pattern of hypertension was for the upper limb pressure to be higher than that in the lower limbs. It seems reasonable to suggest again that these findings reflect incomplete resection of the hypoplastic aortic segment.

The trend of presentation discussed above is continued in our patients above 1 year of age. Thus, only one of 38 patients presented in cardiac failure, and as may be deduced, the greater majority of these patients had isolated juxtaductal coarctation. When operation was performed above 1 year of age, the surgical mortality was, again as expected, considerably lower. Of our 57 patients operated upon above the age of 1, all but one survived. However, it was disturbing to find that 13 of these patients had a raised blood pressure at follow-up. This figure of 23 per cent may be compared with the 30 per cent with residual hypertension in our infantile group. In contrast to this infantile group, most of the older patients had increased lower limb pressures and normal femoral pulses, only 2 of the 13 showing a pressure differential between the upper and lower limbs. Thus, these older patients, several of whom were operated upon under the age of 5 years, showed evidence of systemic hypertension. Rathi and Keith (1964) found that only 20 per cent of their patients operated on over the age of 1 year had residual hypertension, and half of these had pressure differentials between the limbs. Our findings are clearly at variance with these figures, but it must be stated that others have reported persistent systemic hypertension after resection of coarctation (Maron *et al.*, 1973; James and Kaplan, 1974). The study of James and Kaplan (1974) is particularly noteworthy, since they found that of 14 patients operated on between 6 and 16 years of age, 11 had resting systolic blood pressures greater than the 90th centile, the pressures rising to considerably higher levels on exercise.

Thus, our investigation indicates that the increased mortality from early operation must be set against the risk of development of systemic hypertension if operation is delayed. We believe that our findings show that immediate operation is essential when 'complicated' coarctation is encountered in infancy. When operation can be performed as an elective procedure, we suggest that our data indicate the best time for operation to be in the second half of the first year of life. As a corollary to this, we would also suggest that it is important to diagnose coarctation of the aorta within the first year of life, since delay in operation may result in the development of persisting systemic hypertension.

We thank all our colleagues at the Brompton Hospital who have assisted in the diagnosis and care of our patients. We are particularly indebted to Dr. G. A. H. Miller and Dr. K. F. W. Hinson. Dr. Tam was supported by a grant from the Hong Kong Government.

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Comparative efficacy of short-acting and long-acting quinidine for maintenance of sinus rhythm after electrical conversion of atrial fibrillation

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Forty patients with chronic atrial fibrillation, apparently unrelated to any overt heart disease, were randomly allocated to two groups after restoration of sinus rhythm by direct current shock. The patients in group A were given 4 daily doses of quinidine polygalacturonate, while those in group B were given 2 daily doses of a long-acting quinidine preparation, quinidine arabogalactan sulphate.

The percentage of early relapses (within the first month following DC shock) was not significantly different in the two groups: 44·4 per cent in group A and 35 per cent in group B ($P>0·50$). On the other hand, there were fewer late relapses with long-acting quinidine. After 18 months of treatment, 27·8 per cent of patients in group A remained in sinus rhythm, compared with 61 per cent in group B ($P<0·05$).

The average amount of quinidine actually ingested by the patients in group A was smaller than that in group B. However, this could not entirely account for the difference observed in the incidence of relapse since with short-acting quinidine the proportion of patients remaining in sinus rhythm was similar whether the dose was decreased or not. The incidence of gastrointestinal side-effects was the same in the two groups and there were no serious complications that could be attributed to treatment.

It is concluded that long-acting quinidine preparations are more effective than conventional quinidine in preventing late relapses of atrial fibrillation.

While it is usually possible to reverse atrial fibrillation effectively and safely with direct current shock (DC shock) (Lown, 1967), it is more difficult to maintain sinus rhythm. The efficacy of quinidine in the prevention of relapse has been a subject of controversy and, in the opinion of several authors (Oram and Davies, 1964; Killip and Yormak, 1965; Halmos, 1966; Bjerkelund and Orning, 1968; Hall and Wood, 1968; Radford and Evans, 1968; Waris, Kreus, and Salokannel, 1971), this drug does not achieve better results than those observed in the absence of any treatment. However, recent studies by Byrne-Quinn and Wing (1970), Hartel *et al.* (1970), Szekely, Sideris, and Batson (1970), Hillestad *et al.* (1971), and Sodermark *et al.* (1975) have shown the efficacy of long-acting quinidine preparations in preventing relapse. These authors were led to this conclusion by the comparison of two groups of patients, one of which was treated with quinidine and the other with a placebo.

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The purpose of this work was to compare the results obtained, after DC shock, by maintenance therapy with either long-acting or short-acting quinidine.

Subjects and methods

The trial was prospectively conducted in a group of 40 patients admitted to hospital with atrial fibrillation, in whom sinus rhythm had been restored with DC shock (Mathivat, Clément, and Marie-Louise, 1963). In all cases, the arrhythmia had been present for at least 15 days.

The group comprised 29 men and 11 women whose ages ranged from 46 to 81 years, with a mean age of 60·7 years. The arrhythmia had been present for periods ranging from 15 days to 5 years, with a mean duration of 6·4 months. Seven patients had previously undergone one or more conversions by DC shock: in these sinus rhythm had persisted for a mean duration of 3·7 years (range: 7 months to 6 years).

In 26 cases, atrial fibrillation was 'lone'; the patients did not have angina, valve disease, high blood pressure,

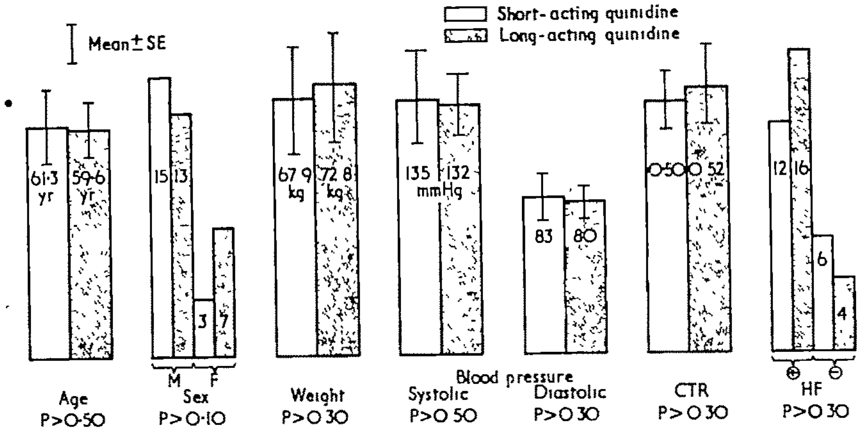

FIG. 1 *Distribution of patients in each group according to age, sex, body weight, blood pressure, cardiothoracic ratio (CTR), and heart failure (HF).*

electrocardiographic abnormalities suggestive of coronary heart disease, or significant enlargement of the heart (McCarthy, Varghese, and Barritt, 1969). In the remaining 14 cases, the cardiothoracic ratio was greater than 0·55 (from 0·56 to 0·70) in 12 and the blood pressure was above 160/100 mmHg (21·3/13·3 kPa) in 2. The arrhythmia had resulted in congestive heart failure in 12 cases.

Digitalis therapy had been discontinued at least 8 days before DC shock and no patient had been given quinidine before conversion. The patients were randomly allocated to two groups, A and B. After DC conversion, those in group A were given quinidine polygalacturonate[1] in a daily dose of 1·1 g (one 0·275 g tablet every 6 hours). The patients of group B received a long-acting quinidine preparation (quinidine arabogalactan sulphate[2]) in a daily dose of 1·1 g, given in two doses (two 0·275 g capsules every 12 hours). The dosage in both régimes corresponds to 0·660 g quinidine base daily. According to Renais, Scebat, and Lenègre (1971), the blood quinidine levels obtained with the two types of quinidine preparation used in the present work are comparable at equal dosage. With a daily dose equivalent to 0·660 g quinidine base, the mean serum quinidine level is around 3 μg/ml (determination by the method of Brodie and Udenfriend, 1943).

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[1] Cardioquine (Laboratory Nativelle).

[2] Longacor (Laboratory Nativelle).

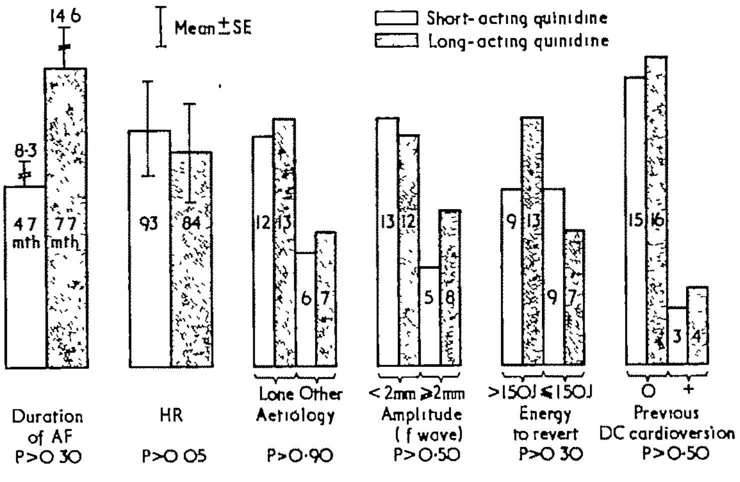

FIG. 2 *Distribution of patients according to duration of atrial fibrillation (AF), heart rate (HR), aetiology (lone AF in contrast to other patients), amplitude of* f *wave, energy of DC shock, and previous cardioversion.*

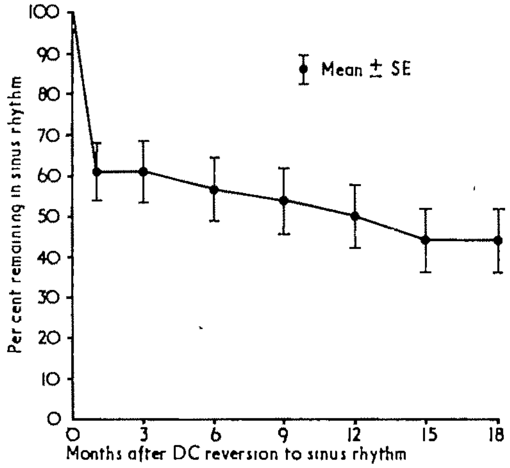

FIG. 3 *Maintenance of sinus rhythm in whole series (38 patients).*

All patients had daily clinical and electrocardiographic examination during the week following the DC shock. After leaving the hospital, they were examined every 3 months for 18 months or until atrial fibrillation recurred. An electrocardiogram was recorded at each visit. No patient was lost to follow-up.

After randomization, 20 patients were included in group A and 20 in group B. For 2 patients, originally in group A, conventional quinidine was replaced by the long-acting preparation after a 15-day and a 6-month treatment period. The change in treatment was made, independently of the result obtained, by the patient's personal physician who was unaware that the choice of the quinidine preparation had been made by randomization. These two patients were still in sinus rhythm when treatment was changed. These two patients were excluded when the results were analysed.

There was no significant difference between the two groups with respect to: age, sex, weight, systolic and diastolic blood pressure, heart rate before DC shock, cardiothoracic ratio, duration of atrial fibrillation, amplitude of *f* waves on the electrocardiogram, energy of the DC countershock, previous DC conversion, aetiology, and incidence of congestive heart failure (Fig. 1 and 2).

The results were expressed by plotting the percentage of patients remaining in sinus rhythm on the Y axis and the time elapsed since DC shock on the X axis. For a given time interval, the percentage of patients remaining in sinus rhythm was derived from the ratio of the number of patients remaining in sinus rhythm at the end of that time interval to the number of patients for whom the duration of follow-up was at least equal to this interval. In 1 case, the administration of long-acting quinidine was discontinued after 7 months even though sinus rhythm still persisted; this case was taken into account only for the assessment of results up to 6 months. One patient treated with long-acting quinidine died after 4 months from intercurrent disease (haemorrhage due to alcoholic cirrhosis); he was included only for the estimation of the percentage of patients still in sinus rhythm up to 3 months.

Results

The results are shown in the Table and Fig. 3 for all patients and in the Table and Fig. 4 for groups A and B separately.

Overall, there was a large proportion of early relapses since only 60 per cent of patients remained in sinus rhythm after 1 month of treatment. These relapses took place between the 2nd and 25th days. After the first month the incidence of relapse was lower and the percentage of patients still in sinus rhythm at 18 months was 44 per cent.

56 per cent of patients in group A and 65 per cent of those in group B remained in sinus rhythm after 1 month of treatment. The difference was not significant ($P > 0{\cdot}50$). On the other hand, the incidence of long-term relapse was lower in the group treated with long-acting quinidine: after 18 months of treatment, 61 per cent of patients in group B remained in sinus rhythm, compared with only 28 per cent in group A ($P < 0{\cdot}05$).

Tolerance of treatment was comparable in the two groups: 1 patient in group A and 2 in group B complained of gastrointestinal symptoms. In one of the latter, the drug had to be discontinued; this was followed by immediate return of the arrhythmia.

Mean heart rate during the follow-up period was 65±14 beats/minute in group A and 67±9 beats/minute in group B. There was no significant

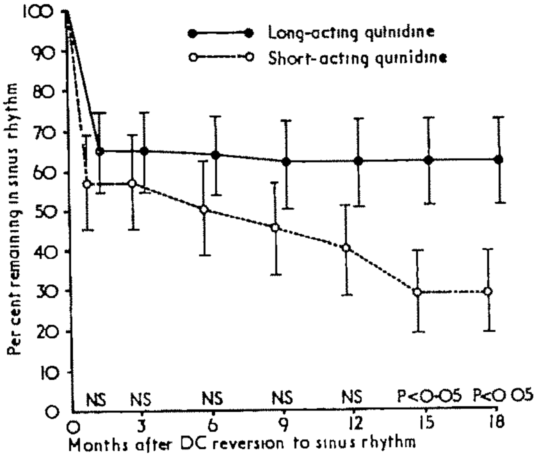

FIG. 4 *Maintenance of sinus rhythm in the two groups of patients.*

TABLE *Effect of quinidine on maintenance of restored sinus rhythm*

Follow-up (mth)	*No of patients*			*Sinus rhythm*			*Atrial fibrillation*			*% sinus rhythm*			*Standard deviation*			
	A+B	*A*	*B*	*A+B*	*A*	*B*	*A+B*	*A*	*B*	*A+B*	*A*	*B*	*A+B*	*A*	*B*	*P*
≥1	38	18	20	23	10	13	15	8	7	50·5	55·6	65·0	7·9	11·7	10·7	>0·50
≥3	38	18	20	23	10	13	15	8	7	50·5	55·6	65·0	7·9	11·7	10·7	>0·50
≥6	37	18	19*	21	9	12	16	9	7	56·8	50·0	63·2	8·1	11·8	11·1	>0·40
≥9	36	18	18†	19	8	11	17	10	7	52·8	44·4	61·1	8·3	11·7	11·5	>0·30
≥12	36	18	18	18	7	11	18	11	7	50·0	38·9	61·1	8·3	11·5	11·5	>0·10
≥15	36	18	18	16	5	11	20	13	7	44·4	27·8	61·1	8·3	10·6	11·5	<0·05
≥18	36	18	18	16	5	11	20	13	7	44·4	27·8	61·1	8·3	10·6	11·5	<0·05

*1 death at 4 months; †treatment discontinued in 1 patient after 7 months.
A, treatment with short-acting quinidine; B, treatment with long-acting quinidine.
P, significance of difference between A and B (% remaining in sinus rhythm).

difference between the two groups with regard to mean duration of QT interval (409±51 ms in group A and 410±33 ms in group B) or QU interval (614±54 ms in group A and 614±40 ms in group B).

The initial dose was reduced more often in group A (10 cases) than in group B (2 cases) ($P<0·005$). In group A, the initial dose of 4 tablets of quinidine polygalacturonate daily was reduced to 3 tablets in 6 patients and to 2 tablets in 4 others. In 4 cases, the dose of quinidine had to be reduced because of quinidine toxicity (excessive prolongation of QT interval) demonstrated on the electrocardiogram; in the other cases, reduction of quinidine dose was decided either by the patient or by his personal physician because of the inconvenience of taking a tablet every 6 hours. In group B, quinidine dose was reduced to 2 capsules daily in 2 cases (on the patient's own initiative in 1 case and in order to adjust the dose to the patient's weight (39 kg) in the other).

Irrespective of the type of treatment, the percentage of patients still in sinus rhythm after 18 months was not significantly different whether dosage was decreased or not. Of the 10 patients in group A in whom dosage was reduced, 4 remained in sinus rhythm at 18 months, compared with 1 only of the 8 patients in whom dosage was unchanged, but the difference was not statistically significant ($P>0·10$). In group B, the 2 patients in whom dosage was decreased remained in sinus rhythm at 18 months.

Discussion

The results of this trial suggest that long-acting quinidine is more effective than short-acting quinidine for the maintenance of sinus rhythm after DC conversion of atrial fibrillation. After 18 months of treatment, sinus rhythm persisted in 61 per cent of patients taking long-acting quinidine compared with 28 per cent of those on the short-acting drug ($P<0·05$). This difference is all the more significant as the choice of treatment was determined by randomization, and the two groups were comparable in all important respects (Fig. 1 and 2). In addition, both groups were relatively homogeneous, since atrial fibrillation was unaccompanied by overt heart disease in most cases.

One-third of the patients treated with short-acting quinidine reduced the dose initially prescribed because of difficulties in the practical conduct of treatment. As a result, the average amount of quinidine actually taken was lower in this group than in that treated with long-acting quinidine.

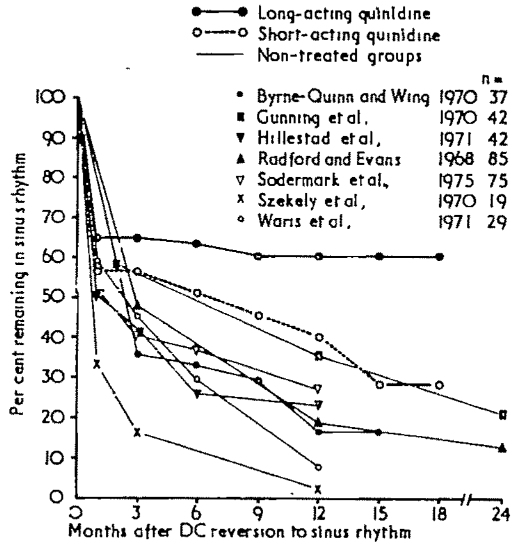

FIG. 5 *Number of patients (%) remaining in sinus rhythm after DC conversion. Comparison with the published data in untreated groups.*

However, this fact could not entirely account for the difference observed in the incidence of relapse, since with short-acting quinidine the maintenance rate of sinus rhythm was similar whether dosage was decreased or not. We did not determine blood quinidine levels systematically. Byrne-Quinn and Wing (1970) and Hillestad *et al.* (1971) were not able to find a correlation between blood quinidine levels and the incidence of relapse.

In this trial, the duration of maintenance of sinus rhythm obtained with short-acting quinidine was similar to that previously reported in the absence of any treatment (Fig. 5) (Radford and Evans, 1968; Byrne-Quin and Wing, 1970; Gunning *et al.*, 1970; Szekely *et al.*, 1970; Hillestad *et al.*, 1971; Waris *et al.*, 1971; Sodermark *et al.*, 1975). At present the efficacy of this therapy in the prevention of relapse after reversion of atrial fibrillation is highly controversial. Indeed, results obtained vary from author to author, ranging from 40 to 68 per cent success rate at 1 year, and from 20 to 53 per cent at 2 years (Killip and Yormak, 1965; Jouve *et al.*, 1966; Morris, Peter, and McIntosh, 1966; Bjerkelund and Orning, 1968; Colin *et al.*, 1968; Hall and Wood, 1968; Waris *et al.*, 1971; Jacques *et al.*, 1973). Sokolow and Ball (1956) considered this therapy effective since, in their experience, relapse of arrhythmia occurred in 85 per cent of cases in the absence of treatment and in only 21 per cent with a daily dose of 1·6 g quinidine. Hurst *et al.* (1964) shared this opinion, for they observed 77 per cent of immediate relapse of atrial fibrillation after discon-continuance of quinidine maintenance therapy. Similarly, Cramer (1968) found a lower incidence of relapse, both early and late, with a daily dose of quinidine equal to or exceeding 1·2 g. On the other hand, Oram and Davies (1964), Halmos (1966), Hall and Wood (1968), and Waris *et al.* (1971) found no significant difference between the results obtained with or without maintenance therapy with short-acting quinidine. It must be pointed out, however, that in none of these studies, whether favourable to the action of quinidine or not, were patients allocated randomly to quinidine or control groups, except that by Oram and Davies (1964).

Most recent comparative trials agree in acknowledging the efficacy of long-acting quinidine preparations in the maintenance of sinus rhythm after conversion of atrial fibrillation. Byrne-Quinn and Wing (1970), in a double-blind trial, obtained a success rate of 16 per cent after 15 months with placebo and 45 per cent with a long-acting preparation of quinidine bisulphate ($P < 0{\cdot}01$). In another randomized trial, Hillestad *et al.* (1971) found that 15 per cent of patients subjected to DC shock remained in sinus rhythm after 1 year in the absence of maintenance therapy, compared with 31 per cent of those given long-acting quinidine ($P < 0{\cdot}05$). The difference was particularly clear cut when the onset of atrial fibrillation was less than 1 year previously. Szekely *et al.* (1970) also obtained a higher success rate with long-acting quinidine than without treatment, in an unrandomized trial. Korsgren *et al.* (1965) found a fairly definite correlation between the duration of the maintenance of sinus rhythm and the assiduity with which quinidine treatment was followed. Very recently, Sodermark *et al.* (1975) in a multicentre controlled study found that after one year 51 per cent of the patients in the quinidine treated group remained in sinus rhythm, compared with 28 per cent in the control group.

On the other hand, Resnekov *et al.* (1969) consider that long-acting quinidine provides no distinct benefit in maintaining sinus rhythm. These authors compared the duration of maintenance of sinus rhythm after two successive DC conversions in the same patients, without maintenance therapy after the first and with long-acting quinidine after the second conversion. It must be pointed out, however, that quinidine therapy was prescribed systematically after the second conversion and not in random order. In addition, mean duration of the maintenance of sinus rhythm observed in this trial suggests that the main goal of the authors was the prevention of the early relapse of the arrhythmia. Gunning *et al.* (1970) found no difference between the long-term results obtained with and without quinidine bisulphate in patients subjected to conversion of atrial fibrillation after cardiac surgery.

Like most authors (Killip and Yormak, 1965; Korsgren *et al.*, 1965; Halmos, 1966; Jouve *et al.*, 1966; Bjerkelund and Orning, 1968; Byrne-Quinn and Wing, 1970; Gunning *et al.*, 1970; Hillestad *et al.*, 1971; Sodermark *et al.*, 1975), we found a high incidence of relapse within the first month of DC shock. This incidence was lower with long-acting than with conventional quinidine (7 or 35% compared with 8 or 44%), but the difference was not significant. These results suggest that the efficacy of the long-acting preparation is reflected mainly in the prevention of long-term relapse; in particular, it was surprising to find that almost all patients who were given this preparation and were still in sinus rhythm after 1 month of treatment, remained so subsequently. In the group given conventional quinidine, the percentage of patients remaining in sinus rhythm decreased progressively after the first month. These findings are similar to those of Hillestad *et al.* (1971) but different from those of Byrne-Quinn and Wing (1970) and Hartel *et al.*

(1970) who found that long-acting quinidine also prevented short-term recurrence.

Some authors have abandoned the use of quinidine to prevent relapse of atrial fibrillation because of the risk of sudden death (Oram and Davies, 1964; Killip and Yormak, 1965; Bjerkelund and Orning, 1968; Radford and Evans, 1968; Waris *et al.*, 1971). This drug is well known for its capacity to induce serious ventricular arrhythmias (Thomson, 1956) and the incidence of these is thought to be directly related to blood quinidine levels (Sokolow and Ball, 1956; Bjerkelund and Orning, 1968). We have observed no such arrhythmias, but had to decrease the dose of conventional quinidine in four cases because of the appearance of a conspicuous quinidine effect on the electrocardiogram. We observed no electrocardiographic changes of this type with long-acting quinidine, because this preparation makes it possible to obtain comparatively stable blood quinidine levels without unduly high peak concentration (Renais *et al.*, 1971; Salvador *et al.*, 1971). Similarly, Gunning *et al.* (1970), Hartel *et al.* (1970), and Hillestad *et al.* (1971), had no deaths that could be attributed to long-acting quinidine. However, Byrne-Quinn and Wing (1970) mentioned a case of sudden death in the course of treatment: it was not proved that this was related to therapy, as it occurred in a patient with severe ischaemic heart disease, though the previous finding of a high blood quinidine level suggests that it may have been. Thus, though accidents seem to be rarer with long-acting quinidine, they nevertheless remain possible.

In conclusion, it follows from this work that long-acting quinidine preparations have several advantages over conventional quinidine. They are more effective in maintaining sinus rhythm after conversion from atrial fibrillation. The convenience of twice daily administration results in their being more readily accepted by patients who therefore follow their treatment more regularly. Lastly, they may reduce the risk of serious arrhythmias by avoiding sharp rises to very high peak levels.

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Comparison of single and biplane ejection fractions in patients with ischaemic heart disease[1]

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Simultaneous biplane left ventriculography was performed in 59 patients with ischaemic heart disease. A comparison was made of the frontal (EFF), lateral (EFL), and biplane (EFB) ejection fractions. Discrepancies between the three measurements in the same patient were frequently observed. The patients were then grouped according to the presence or absence of signs of transmural myocardial infarction in the electrocardiogram or wall motion abnormalities, and the single and biplane EF data were again compared. There were 31 patients with previous transmural myocardial infarction and 37 patients with wall motion abnormalities, usually involving the anterior or inferior walls. The EFL of patients with transmural myocardial infarction or wall motion abnormalities commonly exceeded the EFF, because of frequent preservation of dorsal wall contraction visualized only in the lateral plane. Consequently, there was a significant difference between EFF or EFL and EFB for these patients. In contrast, there was close agreement between EFF and EFL for patients without transmural myocardial infarction or wall motion abnormalities. It is concluded that differences frequently occur between single and biplane EF in patients with ischaemic heart disease, especially if transmural myocardial infarction or wall motion abnormalities are present. Hence, accurate assessment of left ventricular performance is greatly facilitated by simultaneous or sequential biplane ventriculography.

Systolic ejection fraction has recently become an important index of left ventricular performance. It is quoted particularly in the context of coronary artery surgery, where it is used both as a criterion of operability and an index of postoperative myocardial function (Cohn *et al.*, 1974b; Lea *et al.*, 1972). In most cases, the ejection fraction has been calculated from single plane angiograms. Attention is now being drawn to the frequent occurrence of segmental left ventricular wall motion abnormalities in coronary artery disease (Baxley and Reeves, 1971; Cohn, Herman, and Gorlin, 1974) and consequently doubt has been cast on single plane ejection fraction as a reliable index of left ventricular performance (Vogel, Cornish, and McFadden, 1973; Gentzler *et al.*, 1973). We have, therefore, analysed our data obtained from biplane angiography in 59 patients evaluated for angina pectoris or heart failure. An attempt was made to seek any parameter that might predict the accuracy of single plane ejection fraction in the individual patient.

Methods

Fifty-nine biplane left ventricular (LV) cineangiocardiograms were obtained from patients evaluated for angina pectoris or heart failure in the cardiac catheterization laboratory. All patients had resting electrocardiograms performed before the procedure.

Premedication was with 100 to 200 mg oral pentobarbitone and 0·6 mg atropine given subcutaneously. All patients underwent selective coronary arteriography by the Judkins technique, with multiple oblique views as the initial part of the procedure. After this, the left ventricle was entered with a 'pigtail' catheter and 40 to 60 ml Renografin 76 was injected under pressure into the left ventricular cavity. The ventriculogram was recorded on 35 mm cine film, in the frontal and lateral projections simultaneously, at 64 frames per second.

The LV cineangiogram was later projected on either a Vanguard rear display or a Tagarno frontal display system. Optimal end-systolic and end-diastolic frontal and their corresponding lateral frames were selected, eliminating both premature ventricular contractions and the first following beat. Biplane ventricular volumes were calculated either by hand planimetry or by a recently developed semiautomated computer system (Pai, Fozzard, and Brooks, 1974). In the former case, the selected ventricular silhouettes were traced, the areas planimetered, and the long axes measured.

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Biplane end-systolic and end-diastolic volumes were then calculated according to the area-length method of Dodge using the formula (Dodge *et al.*, 1960):

$$V_t = 0{\cdot}78 \times \frac{(CF_m)^2\,(CF_s)\,A_a\,A_l}{L_s} - 3{\cdot}8 \qquad \text{(a)}$$

Where V_t = true biplane volume (ml)
CF_m = correction factor for non-parallel *x*-ray distortion on the projection with the greatest major axis
CF_s = correction factor in the other projection
A_a = area of the projected image in the anteroposterior view (cm^2) uncorrected
A_l = area of the projected image in the lateral view (cm^2) uncorrected
L_s = the shortest of the two measured long axes.

The biplane ejection fraction (EFB) was obtained from the formula:

$$EFB = \frac{EDV - ESV}{EDV}\,\% \qquad \text{(b)}$$

Where ESV = end systolic volume
EDV = end diastolic volume.

Single plane (either frontal or lateral) ejection fraction (EFS) was calculated using the formula:

$$EFS = 1 - \left[\frac{L_D}{L_S} \times \left(\frac{A_S}{A_D}\right)^2\right] \times 100\% \qquad \text{(c)}$$

Where L_D = long axis in diastole (cm)
L_S = long axis in systole (cm)
A_S = area of projected image in end-systole
A_D = area of projected image in end-diastole.

When the computer system was used, a hypersonic Graf-pen digitizer was used to trace the desired ventricular silhouettes and thus enter the digitized left ventricular boundary co-ordinate data into a PDP-11 minicomputer system. The ventricular volume analysis programme displayed the digitized image on a cathode ray storage tube and permitted the image either to be accepted or rejected and retraced. The computer programme then used the ventricular boundary co-ordinate data to compute the long axis of the left ventricle, area enclosed by LV contour by integration, biplane ventricular volumes using Dodge's formula (a), biplane ejection fraction by formula (b), and single plane ejection fraction using formula (c).

Wall motion analysis was performed by superimposing end-systolic and end-diastolic frames using the midpoint of the aortic valve as the fixed point of reference. This was done either by hand or using the computer generated displays of superimposed digitized systolic and diastolic contours on the storage oscilloscope. The ventricular outline was divided into three segments in each plane: 1) frontal: anterolateral, apical, and inferior; 2) lateral: anterior, inferior, and dorsal. These segments were then examined qualitatively for wall motion abnormalities during systole.

Results

Angiographic analysis

The coronary arteriographic, electrocardiographic, and ventriculographic findings for the 59 patients are listed in Tables 1 and 2. Seven patients were normal in all these respects, 51 had coronary artery disease shown on the coronary arteriogram, and one patient had congestive cardiomyopathy with normal coronary arteries.

The distribution of major lesions (greater than 70% stenosis) in the 51 patients with coronary artery disease was as follows: 82 per cent had major lesions in the left anterior descending artery, 59 per cent in the right coronary artery, and 57 per cent in the main left circumflex coronary artery or one of its lateral branches. Three patients had additional major stenosis of the left main coronary artery.

Thirty-seven patients (63%) had wall motion abnormalities on the left ventriculogram. If those patients with normal coronary arteries were excluded, the proportion rose to 73 per cent.

The close relation between wall motion abnormalities and transmural myocardial infarction was shown by the fact that 27 of 31 patients (87%) with electrocardiographic evidence of transmural myocardial infarction showed segmental wall motion abnormalities on the left ventriculogram. The 27 patients comprised all 9 patients with anterior and inferior transmural myocardial infarction, 10 of the 11 patients with anterior transmural myocardial infarction, and 8 of the 11 patients with inferior transmural myocardial infarction. These data contrasted with the low incidence of wall motion abnormalities in patients with normal electrocardiograms or with nontransmural myocardial infarction. Wall motion abnormalities were present in 5 of 18 patients with normal electrocardiograms and 1 of 4 patients with nontransmural myocardial infarction.

Of the 4 remaining patients with wall motion abnormalities, 2 had electrocardiographic criteria for left ventricular hypertrophy and 2 had left bundle-branch block. Both patients with left bundle-branch block had severe triple vessel disease.

The locations of the wall motion abnormalities in these 37 patients are given in Table 1. Abnormalities in the anterior or apical segments were seen in almost all cases. The inferior wall was less commonly involved and the dorsal (or posterior) ventricular wall was the site of wall motion abnormalities in only 33 per cent of the cases. The location of the wall motion abnormality usually corresponded to regions supplied by severely stenotic or occluded coronary arteries.

TABLE 1 *Electrocardiographic, coronary arteriographic, ventriculographic findings and single and biplane ejection fractions of patients with wall motion abnormalities*

Case No.	*Electrocardiogram*	*Coronary arteriogram**				*Left ventriculogram†*				*Ejection fraction (%)*		
		LAD	*LCX*	*RCA*	*LMC*	*Ant*	*Api*	*Inf*	*Dorsal*	*Biplane*	*Frontal*	*Lateral*
1	Anterior (transmural)	2	1	2	0	H	H	N	N	70	59	70
2	Inferior (transmural)	2	2	1	0	N	H	H	N	61	42	70
3	Anterior (transmural)	3	0	0	0	A	A	P	N	31	27	42
4	Anterior (transmural)	3	2	3	0	H	A	H	N	36	38	50
5	Anterior (transmural)	2	2	2	0	H	A	H	N	42	49	40
6	Ant–inf (transmural)	3	2	2	0	H	H	H	H	41	28	45
7	Normal	0	2	1	0	H	N	N	N	59	60	55
8	Inferior (transmural)	1	3	3	0	H	A	A	H	28	33	39
9	Normal	0	0	3	0	H	N	N	N	47	49	43
10	Ant–inf (transmural)	3	2	2	0	H	H	H	H	29	21	32
11	Inferior (transmural)	2	2	2	0	N	N	H	N	71	65	73
12	Ant–inf (transmural)	2	1	0	0	A	A	H	N	18	07	37
13	Anterior (transmural)	3	2	0	0	A	A	A	N	12	12	17
14	Anterior (non-transmural)	3	0	3	0	H	H	H	H	14	19	15
15	Normal	2	3	1	2	H	H	H	N	59	46	62
16	Inferior (transmural)	0	2	3	0	H	A	A	N	36	37	47
17	Anterior (transmural)	3	1	1	0	H	P	A	H	23	37	20
18	Ant–inf (transmural)	3	3	3	0	H	H	A	N	19	19	26
19	Ant–inf (transmural)	3	1	3	0	N	H	H	H	27	42	17
20	Inferior (transmural)	2	2	1	0	H	N	N	N	63	58	63
21	LVH	0	2	2	0	A	H	H	N	32	25	26
22	LBBB	2	2	3	0	A	H	H	H	25	29	16
23	Normal	2	1	2	0	H	N	H	N	40	47	44
24	Inferior (transmural)	2	3	3	2	A	H	H	H	38	27	34
25	Ant–inf (transmural)	3	2	3	0	H	H	A	H	25	21	23
26	Inf (transmural), and ant (non-transmural)	2	2	2	0	N	N	H	N	72	72	67
27	Anterior (transmural)	3	0	1	0	A	H	N	N	34	31	54
28	LVH	0	0	0	0	A	H	H	H	21	23	15
29	Ant–inf (transmural)	2	1	3	0	H	H	H	N	21	29	35
30	Anterior (transmural)	3	1	3	0	H	H	H	H	30	31	31
31	LBBB	2	2	3	0	A	H	H	N	08	09	21
32	Anterior (transmural)	1	1	3	0	A	H	H	N	25	17	45
33	Ant–inf (transmural)	3	2	1	0	A	H	A	N	13	14	21
34	Inferior (transmural)	2	2	1	0	H	N	H	N	59	51	61
35	Normal	3	0	0	0	H	N	N	N	75	71	72
36	Anterior (transmural)	3	0	1	0	A	H	H	N	44	36	50
37	Ant–inf (transmural)	3	2	3	0	H	H	H	H	47	39	52

Abbreviations

* Coronary arteriogram: LAD = left anterior descending artery, LCX = left circumflex artery, RCA = right coronary artery, LMC = left main coronary artery, 3 = occlusion, 2 = >70 per cent stenosis, 1 = <70 per cent stenosis, 0 = normal.

† Left ventriculogram: Ant = Anterior, Api = Apical, Inf = Inferior, N = normal, H = hypokinesia, A = akinesia, P = paradoxical.

Ejection fraction analysis

Table 3 lists the mean single and biplane ejection fractions for all patients and for the subgroups with or without previous transmural myocardial infarction or wall motion abnormalities. Patients with a history of previous myocardial infarction or with documented wall motion abnormalities tended to have low ejection fractions, while those without these features tended to have normal ejection fractions.

The single and biplane ejection fraction data for each patient are given in Tables 1 and 2. Comparison of frontal (EFF), lateral (EFL), and biplane (EFB) ejection fractions for the same patients frequently revealed significant differences between frontal and lateral plane measurements and between single and biplane measurements.

The data were subjected to further analysis in an effort to explain these discrepancies. Each case was examined for the presence or absence of electrocardiographic evidence of transmural myocardial infarction, and of wall motion abnormalities. The results are presented in Tables 1 and 2 and displayed graphically in Fig. 1 and 2.

A consistent discrepancy between frontal and lateral plane measurements in patients with either transmural myocardial infarction or wall motion abnormalities was observed. In most cases higher values were obtained for the lateral plane than for the frontal plane measurement. The mean EFF for patients with myocardial infarction was 39·7±3·8 per cent and the mean EFL was 46·7±3·7 per cent (P<0·0025). Similarly, the mean EFF for patients with wall motion abnormalities was 35·5±2·8 per cent, while the mean EFL was 41·5±3·0 per cent (P<0·005).

Biplane ejection fractions tended to be intermediate between the frontal plane and the lateral plane ejection fraction in the patients with myocardial infarction or wall motion abnormalities. The differences between EFF or EFL and EFB for these groups were statistically significant (Table 3).

Differences between single and biplane ejection fractions were also seen in patients with no previous myocardial infarction or whose ventriculograms showed no abnormally contracting segments. However, when the magnitude and the range of differences between single and biplane measurements for these patients were examined, both smaller discrepancies and less scatter of values were noted. These observations are illustrated graphically in Fig. 1 and 2, where biplane ejection fraction is plotted against frontal and lateral plane ejection fraction respectively. The standard error for the regression (Syx) of EFB on EFF of the patients with myocardial infarction or wall motion abnormalities was in both cases 7·8. Patients without either of these features had considerably smaller

TABLE 2 *Electrocardiographic, coronary arteriographic findings and single and biplane ejection fractions of patients without wall motion abnormalities*

Case No.	*Electrocardiogram*	*Coronary arteriogram*				*Ejection fraction (%)*		
		LAD	*LCX*	*RCA*	*LMC*	*Biplane*	*Frontal*	*Lateral*
38	Normal	0	0	0	0	79	72	80
39	Normal	0	0	0	0	90	90	86
40	Anterior (non-transmural)	2	2	2	0	77	75	75
41	Anterior (non-transmural)	1	0	0	0	87	84	86
42	Normal	2	0	1	0	80	78	81
43	Normal	2	2	2	0	86	85	83
44	Normal	2	3	1	0	79	81	75
45	Normal	2	1	1	0	60	65	62
46	Inferior (transmural)	2	0	2	0	77	74	72
47	Normal	0	0	0	0	70	75	57
48	Normal	0	0	0	0	83	75	88
49	Anterior (transmural)	3	1	1	0	74	72	78
50	Normal	2	1	0	0	84	79	81
51	Normal	2	1	0	1	75	79	71
52	Normal	0	0	0	0	66	60	67
53	Normal	1	1	0	2	80	83	75
54	RBBB	0	0	0	0	72	70	66
55	LVH	0	2	3	0	90	84	91
56	Inferior (transmural)	2	2	3	0	91	85	91
57	Anterior (non-transmural)	2	2	3	0	84	79	84
58	Inferior (transmural)	2	2	2	0	82	84	72
59	Normal	0	0	0	0	82	80	79

Abbreviations as in Table 1.

TABLE 3 *Mean value of single and biplane ejection fractions for different patient subgroups*

	No.	*EFB*	*EFF*	*EFL*	*EFB vs. EFF*	*EFB vs. EFL*	*EFF vs. EFL*
All	59	53·3 (±3·3)	51·3 (±3·2)	54·8 (±3·0)	P<0·0125	NS	P<0·01
Transmural myocardial infarction	31	42·3 (±4·0)	39·7 (±3·8)	46·7 (±3·7)	P<0·01	P<0·005	P<0·0025
No transmural myocardial infarction	26	70·3 (±3·7)	68·6 (±3·6)	68·2 (±3·9)	P<0·05	P<0·01	NS
Wall motion abnormalities	37	37·5 (±3·0)	35·5 (±2·8)	41·5 (±3·0)	P<0·05	P<0·005	P<0·005
No wall motion abnormalities	22	79·5 (±1·7)	77·7 (±1·5)	77·3 (±1·9)	P<0·025	P<0·025	NS

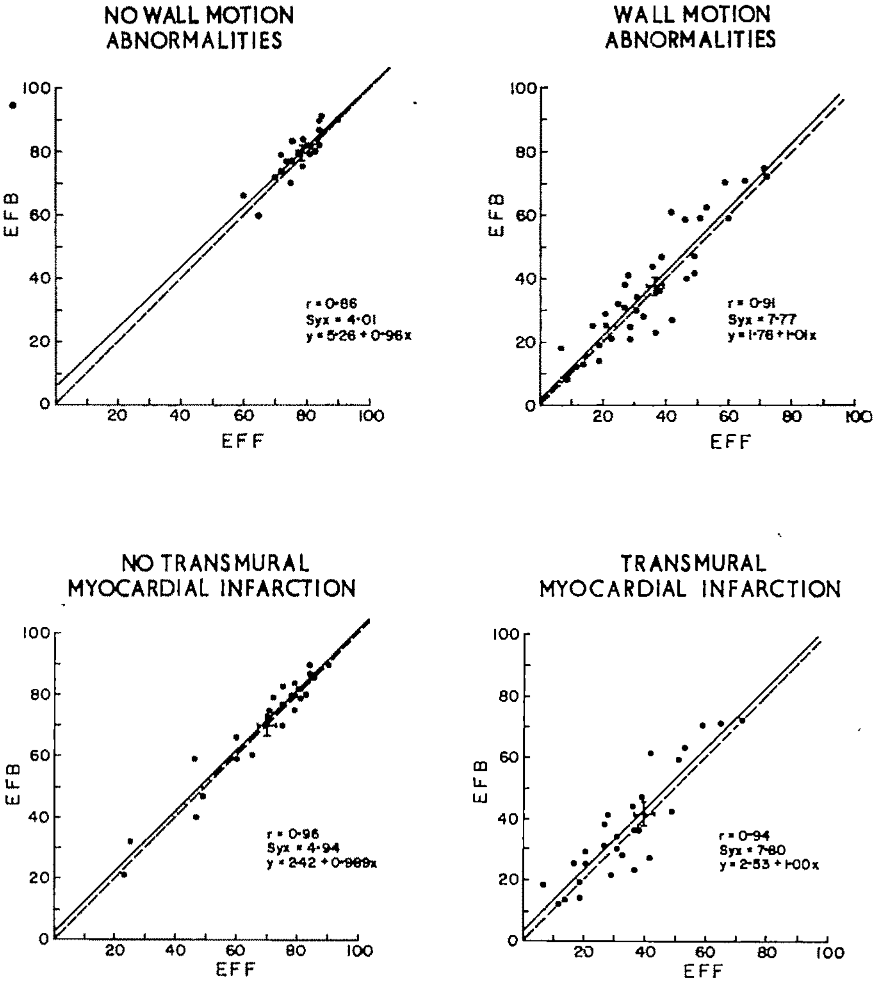

FIG. 1 *Relation between the frontal plane and biplane ejection fractions in patients with and without wall motion abnormalities, and with and without the electrocardiographic pattern of previous transmural myocardial infarction. The mean and standard error of the mean are marked by cross-bars. Broken line=identity line. Continuous line=regression line. r=correlation coefficient. Syx=standard error of the regression.*

standard errors of 4·9 and 4·0, respectively. Similarly, the standard error for the regression of EFB on EFL for patients with myocardial infarction and for patients with wall motion abnormalities was 8·0. In contrast patients without previous infarction and without wall motion abnormalities had standard errors of 3·8 and 3·7 respectively.

Discussion

A strong relation between electrocardiographic evidence of transmural myocardial infarction (Q waves present) and the presence of regional wall motion abnormalities has been confirmed in this series (Miller *et al.*, 1975; Williams *et al.*, 1973). Areas of myocardial necrosis or fibrosis are unable to shorten normally resulting in akinetic or dyskinetic segments. Though Q waves are a generally reliable predictor of wall motion abnormalities, the absence of Q waves or even a normal electrocardiogram did not exclude the presence of regional wall motion abnormalities in a small number of patients.

It will be seen from the data presented that single plane EF may be a poor predictor of biplane EF in patients with coronary artery disease. Only in the group of patients without previous transmural myocardial infarction or wall motion abnormalities was there a reasonable correlation between single plane and biplane EF.

The difference between single plane and biplane EF in the series as a whole resulted directly from the often large differences between frontal plane EF and lateral plane EF in those patients with previous myocardial infarction and/or wall motion abnormalities. In both groups the lateral plane EF usually exceeded the frontal plane EF.

Why may there be such a discrepancy between frontal and lateral plane ejection fractions? The explanation lies in the relation between the particular segment of the left ventricle viewed angiographically and its corresponding arterial blood supply. It has been noted that the left anterior descending and right coronary artery are the most commonly diseased coronary arteries (Proudfit, Shirey, and Sones, 1967). These arteries supply the anterolateral, apical, and inferior walls of the left ventricle, which are best represented on the frontal plane or shallow right anterior oblique ventriculogram. The blood supply of the dorsal wall of the left ventricle is usually from the main circumflex coronary artery and its atrioventricular branch. Abnormally contracting segments are less common in the dorsal wall because of its proximal

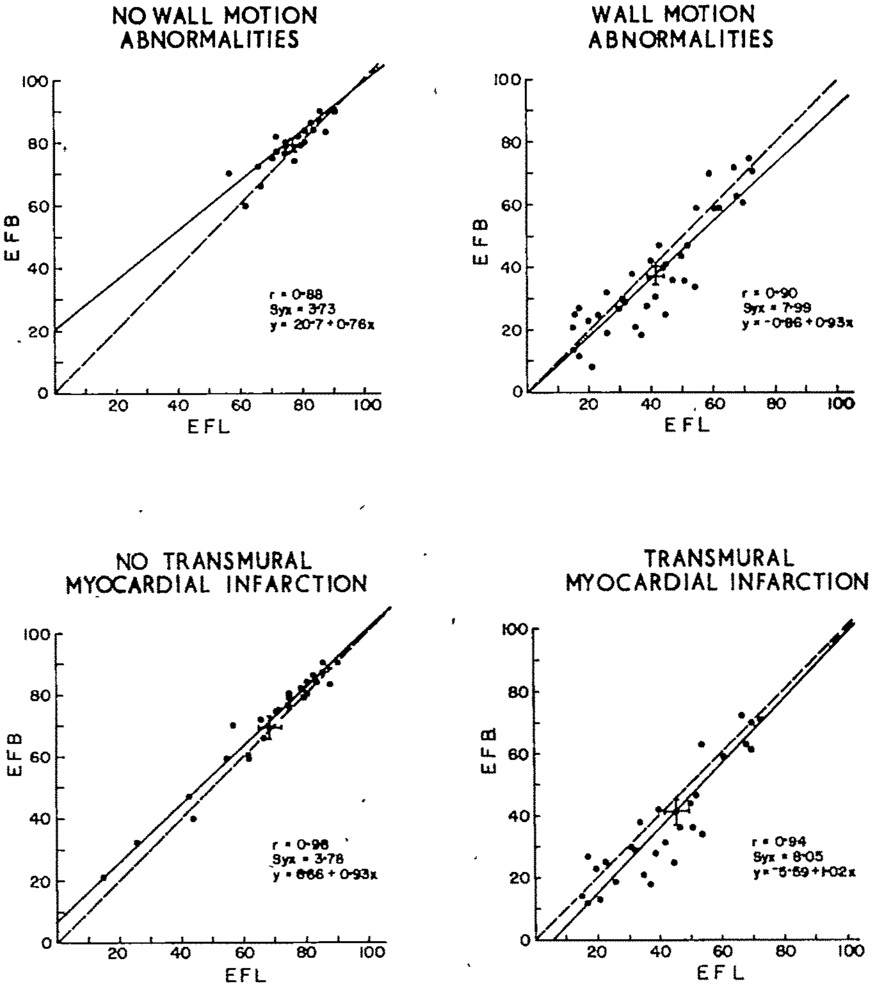

FIG. 2 *Relation between the lateral and biplane ejection fractions in the same groups of patients as in Fig. 1.*

blood supply, the lower incidence of atherosclerotic lesions in the circumflex artery, and the frequent presence of proximal collateral circulation. The dorsal wall of the left ventricle hardly appears in the frontal or shallow right anterior oblique projection, but is seen well in the lateral view. Therefore the contribution of a well-contracting dorsal wall to left ventricular ejection will tend to increase the lateral plane EF which therefore exceeds the frontal plane EF in patients with wall motion abnormalities.

For similar reasons, transmural infarction is far more common in the anteroseptal, anterolateral, and inferior walls, than in the dorsal wall of the left ventricle. Because transmural myocardial infarction is strongly associated with wall motion abnormalities in the infarcted region, patients with transmural myocardial infarction will also tend to show this difference between single and biplane EF. This observation has clinical importance, because it suggests that it is possible to predict, before catheterization, a group of patients where one single plane LV angiogram alone may not provide an accurate index of left ventricular performance. In these patients, reliable evaluation of left ventricular performance would require either a second angiogram in a different plane or simultaneous biplane angiography.

An example of the clinical significance of ejection fraction data presented is given by Case 2 (Table 1). This patient, who had previously sustained a transmural inferior myocardial infarction, had angina. The coronary angiograms showed major two-vessel disease and the left ventriculogram showed a large abnormally contracting inferoapical segment. Since the clinical decision whether this patient was suitable for coronary artery surgery depended not only on the severity of his symptoms and the state of his distal coronary arteries, but also on the left ventricular performance as a major determinant of operative risk, the latter was assessed by measurement of the ejection fraction. This patient had a frontal plane ejection fraction of 42 per cent. If only the frontal EF was available it might have been concluded that the operative risk was too high and that therefore medical management of his angina might be preferable. However, the lateral plane EF was within normal limits at 70 per cent, and the calculated biplane EF was 61 per cent. With this additional information a more accurate assessment of ventricular performance was available when the selection of surgical or medical therapy was made in this individual patient.

Differences between single plane and biplane volume and ejection fraction measurements have recently been reported by three other groups. Cohn *et al.* (1974a) compared single plane 30° right anterior oblique (RAO) ventriculograms with biplane ventriculograms taken 30° RAO and 60° left anterior oblique (LAO). They found a good correlation between single plane and biplane measurements for the minor diameters, ventricular volumes, and ejection fractions, in patients with and without coronary disease who had normally contracting ventricles. This relation was not so apparent in the patients with ventricular wall motion abnormalities, where there was a wider scatter of values for these parameters. The 60° LAO provides a similar view of the ventricle to the lateral projection and thus gives an indication of inferoseptal and dorsal wall contraction not seen in the RAO. Vogel *et al.* (1973) also compared single plane RAO 30° ventriculograms with biplane ventriculograms in RAO 30° and LAO 60° projections. They particularly noted frequent underestimation of the ejection fraction in the RAO projection compared with the biplane measurement in patients with coronary artery disease. This is in agreement with our results. They also pointed out that erroneous conclusions concerning the efficacy of myocardial revascularization could be drawn if pre- and postoperative single plane ejection fractions were compared in the same patient. In some patients single plane EF improved but biplane EF deteriorated; the converse was also seen. Gentzler and his colleagues (1973) compared single plane volume and ejection fraction measurements calculated from the frontal and lateral plane projections in patients with myocardial infarction. Their results obtained differed from our data and those of Vogel *et al.* (1973); in their patients the lateral ejection fraction was considerably less than the frontal ejection fraction. Furthermore, the measured extent of minor equatorial fibre shortening was also less in the lateral plane. The reason for these conflicting results is not clear from the data presented.

Conclusions

It may be concluded on the basis of the data presented that: 1) in the absence of wall motion abnormalities or previous myocardial infarction there is a close correlation between ejection fractions measured in the frontal and lateral planes; 2) in the presence of wall motion abnormalities or a previous transmural myocardial infarction, the ejection fraction measured in the lateral plane usually exceeds that measured in the frontal plane and, consequently, the frontal plane EF tends to underestimate and the lateral plane EF to over-estimate biplane ejection fraction; and 3) accurate angiographic assessment of ventricular performance in patients with coronary artery disease is greatly facilitated by simultaneous or sequential biplane ventriculography, especially if there is electrocardiographic evidence of previous myocardial infarction.

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Relation between craniocerebral injury and subsequent myocardial fibrosis and heart failure
Report of 3 cases

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The findings at necropsy in three cases of severe craniocerebral injury associated with unconsciousness are reported with special reference to the histopathological findings in the myocardium.

In the first case, death occurred 3 days after the trauma, in the second case 21 days after, and in the third case, 7 years after. Necropsy showed myocardial lesions of recent origin in the first case, stromal condensation in the myocardium in the second, and cardiac hypertrophy with coexisting patchy fibrosis of the myocardium in the third. The relation between craniocerebral injury and subsequent myocardial fibrosis is discussed.

Myocardial lesions of recent origin are found fairly often at necropsy in patients who died from certain types of intracranial disease or craniocerebral injury. These lesions have included eosinophilic degeneration and focal necrosis of the myocardium (Shkhvatsabaya, 1961), focal myocardial oedema, necrosis of myofibrils, and interstitial haemorrhage (Eichbaum and Bissetti, 1966), inflammation (Plueckhahn and Cameron, 1968), focal myocytolysis, fuchsinophilic degeneration (Connor, 1969), and myofibrillar degeneration (Reichenbach and Benditt, 1970). The main findings at necropsy were cerebral haemorrhage, cerebral abscesses, thrombosis of cerebral vessels, meningitis, ruptured aneurysm, cerebral infarction, craniocerebral injury, and primary or secondary brain tumours.

Chronic heart lesions such as myocardial fibrosis and cardiac hypertrophy may develop from recent myocardial lesions of encephalogenic origin. However, little attention has hitherto been given to this possibility.

The findings in the 3 cases reported below further substantiate the relation between craniocerebral injury and myocardial fibrosis.

Patients and methods

The records of patients with craniocerebral injury on whom necropsy was performed at this institute were reviewed with special reference to the past history and age at the time of death. The available information about the past history, especially about previous cardiac disease or conditions that might have harmed the heart, is generally more detailed and reliable in cases of young adults than in those of older patients. The ages of the 3 patients presented were 25, 15, and 15 years, respectively, at the time of death. Their histories were therefore studied in more detail and were considered to be sufficiently interesting, particularly in relation to the problems discussed in this paper.

Blocks of brain, lung, liver, kidney, anterior wall of the right ventricle, septum, anterior and posterior wall of the left ventricle and papillary muscles were fixed in 4 per cent neutral formaldehyde solution for from 24 to 36 hours and thereafter embedded in paraffin. Sections 5 μm thick were cut from all tissues and stained with haematoxylin-eosin and van Gieson. Sections from the myocardium were in addition stained with PAS and Mallory's PTAH, and in one case (Case 3) also with Weigert's resorcin fuchsin elastic stain, Best's carmine, Congo red, and Clarck's scharlach R stain (Armed Forces, Institute of Pathology, 1960).

The Table shows the principal microscopical findings in the heart, together with the length of the interval between craniocerebral injury and death of the patients.

Mononuclear and polynuclear leucocytic infiltration of the myocardium, myocytolysis, and myocardial fibrosis, respectively, were graded as follows:

Mononuclear and polynuclear leucocytic infiltration
+ = presence of solitary cells around vessels or between muscle fibres;
++ = presence of clusters of leucocytes around vessels or between muscle fibres;
+++ = more or less diffuse infiltration of the entire myocardium.

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TABLE *Histopathological findings in heart in three cases of craniocerebral injury*

Case No.	*Interval between injury and death*	*Macroscopical findings*	*Microscopical findings*			
			Myocytolysis	*Mononuclear cell infiltration*	*Polymorphonuclear leucocyte infiltration*	*Myocardial fibrosis*
1	3 days	Subendocardial haemorrhage	+++	+++	+	—
2	21 days	Subendocardial haemorrhage	++	++	±	+
3	7 years	Cardiac hypertrophy and fibrosis	+	+	—	+++

For explanation of symbols see *Patients and methods*, pp. 396 and 397.

Myocytolysis

+ = presence of solitary cells showing myocytolysis;
++ = presence of foci of several cells showing myocytolysis;
+++ = a large number of foci of cells showing myocytolysis.

Myocardial fibrosis

+ = presence of loose granulation tissue in interstitial spaces, around vessels, or foci of such tissue—that is, evidence of stromal condensation;
++ = presence of small foci of dense collagenous tissue;
+++ = numerous foci of collagenous tissue scattered throughout the myocardium which were even visible macroscopically.

Case reports

Case 1

The patient, a woman aged 25 years, was thrown off a horse and struck her head. A few minutes after her fall she fainted and was immediately taken to hospital. On admission she was unconscious, her pupils were fixed, but focal neurological signs were absent. A few hours after her admission the blood pressure rose from 130 mmHg (17·3 kPa) systolic and 90 mmHg (12·0 kPa) diastolic to 260 mmHg (34·6 kPa) systolic and 130 mmHg (17·3 kPa) diastolic. She was given dexamethasone and mannitol and this resulted in a fall of the blood pressure to 90 mmHg (12·0 kPa) systolic and 60 mmHg (8·0 kPa) diastolic. Leads I and III of the electrocardiogram showed sinus rhythm and ventricular extrasystoles.

The patient was deeply unconscious, with no reflexes, and despite three days on the respirator, she died. Necropsy disclosed a haematoma in the occipital region, copious subdural haemorrhage, cerebral oedema, and signs of compression of the brain-stem. The heart weighed 300 g. There was evidence of slight subendocardial haemorrhage beneath the left aortic valve.

Microscopical examination of the myocardium showed interstitial oedema, focal necrosis of myofibrils, minute haemorrhages and round cell infiltration perivascularly and diffusely in the interstices. The changes were widespread, being most pronounced beneath the endocardium and within the papillary muscles. There was infiltration with inflammatory cells, the majority being mononuclear cells, granulocytes being scarce. There were no vascular changes or signs of fibrosis (Fig. 1 and 2). The other findings were normal. Death was attributed to compression of the brain resulting from tearing of the communicating veins of the subdural space (Brückenvenen) caused by the injury to the skull.

Case 2

The patient, a girl aged 15 years, hit her head when falling down a flight of stairs. Immediately after her fall she was dazed. A few hours later she became deeply unconscious and was taken to hospital. As there were no focal neurological symptoms her condition was attributed to some form of intoxication. A few hours after admission her blood pressure rose, the pupils were unequal, and Babinski's sign was positive on the right side. The electrocardiogram showed no abnormality. While being transferred to the neurosurgical department her respiration ceased. She was intubated. After 21 days' treatment on the respirator she died.

Necropsy disclosed fracture of the skull in the right parieto-occipital region and epidural haematoma: the brain tissue was soft and discoloured. The heart weighed 190 g. There were macroscopical subendocardial haemorrhages within the upper part of the septum below the aortic valve. Microscopical examination of the myocardium showed focal oedema, necrosis of solitary myofibrils, minute haemorrhages, diffusely and perivascularly stromal condensation, inflammatory cells, which were predominantly mononuclear in type, fibroblasts, fibrocytes, solitary macrophages, and granulocytes (Fig. 3); the other findings were normal. Death was attributed to compression of the brain as a result of fracture of the skull and epidural haematoma.

Case 3

The patient, a boy aged 8 years, collided with a motor-car when cycling. On admission to a neurosurgical unit he was unconscious. He had several convulsive fits and episodes of opisthotonus. Radiography of the skull showed a fracture of the fronto-occipital region with no depression of bone fragments. Angiography of the carotid artery showed an expansive process above the tentorium of the left side.

The patient was placed on the respirator and was given dexamethasone and mannitol. After a few days he regained consciousness and was removed from the respirator. The only available information about the condition of the cardiovascular system dated from the 13th day after his accident. On that occasion the heart

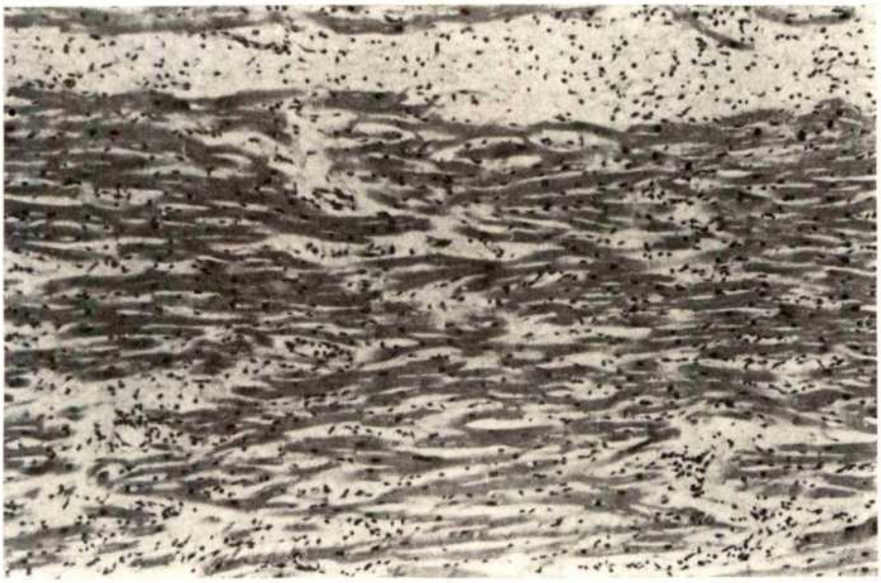

FIG. 1 *Case 1. Photomicrograph showing extensive infiltration with inflammatory cells, predominantly mononuclear in type, and wide separation of myocardial fibres indicating interstitial oedema. (Haematoxylin-eosin. × 80.)*

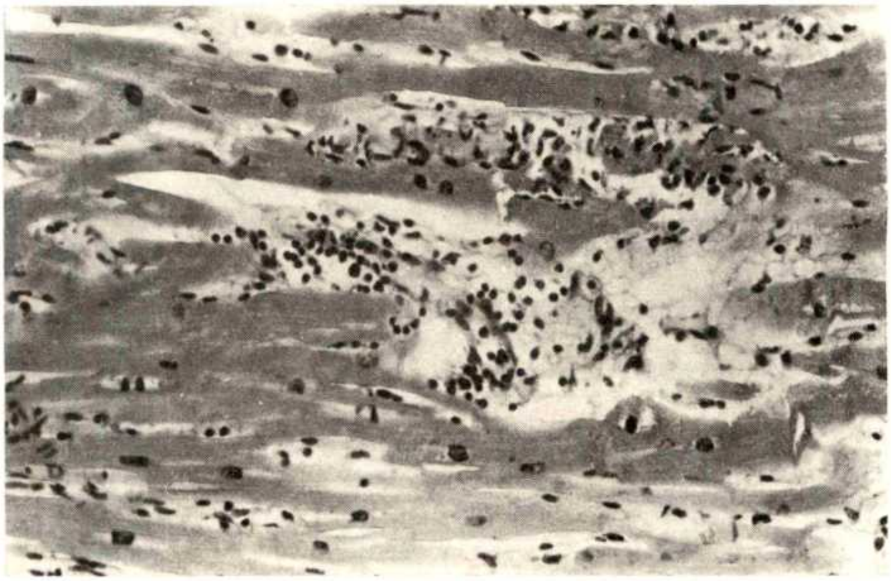

FIG. 2 *Case 1. Photomicrograph showing focal necrosis of myofibrils. (Haematoxylin-eosin. × 200.)*

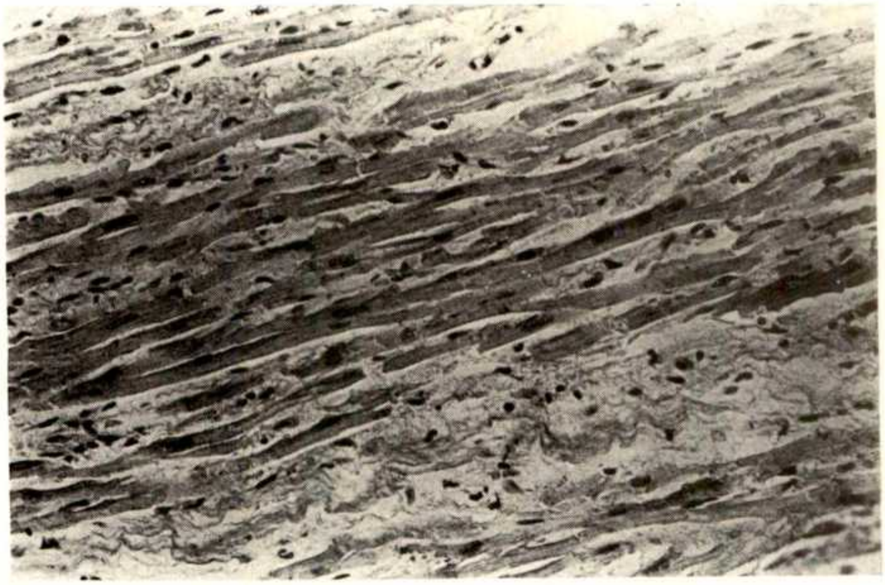

FIG. 3 *Case 2. Photomicrograph showing stromal condensation in myocardium in form of proliferation of fibroblasts and deposition of collagenous fibres 21 days after trauma. (Haematoxylin-eosin. × 200.)*

rhythm was regular, the heart sounds were clear, the pulse rate was 120/min, and the blood pressure was 105 mmHg (14·0 kPa) systolic and 75 mmHg (10·0 kPa) diastolic. Electrocardiograms were not taken. After discharge he was able to attend school and engage in his normal spare-time occupations.

At the age of 9 years he had measles. He was ill for three weeks and was cared for at home. At the age of 11 years he had a mild form of scarlatina. He was followed up by the school medical officer at regular intervals for 7 years after his accident. The clinical and laboratory findings were always normal with no symptoms suggestive of epilepsy. At the age of 15 years, after a short sprint, he suddenly collapsed and died.

At necropsy large punched-out yellow areas denuded of their meningeal covering (*plaques jaunes*) were found in both temporal regions. There was no cerebral oedema; neither were there any bite marks on the tongue. The heart was enlarged, weighing 340 g (body weight was 55 kg). There was pulmonary congestion; the myocardium showed patchy fibrosis; the valves, endocardium, and coronary arteries were normal. Microscopical examination of the myocardium revealed perivascular and focal fibrosis, hypertrophic and atrophic fibres, and minute areas of myocytolysis. There was infiltration with a few mononuclear inflammatory cells, mostly histiocytes (Fig. 4 and 5). No giant cells or granulomas were seen. The walls of the small arterial branches were thickened and fibrosed with slight endothelial proliferation. Staining with Best's carmine and Congo-red for evaluation of glycogen and amyloid was negative; there was no accumulation of lipids in the sarcoplasm. Microscopical examination of lungs, liver, spleen, and kidneys was normal.

The immediate cause of death was considered to be acute cardiac insufficiency resulting from fibrosis of the myocardium.

Discussion

To elucidate whether the craniocerebral injury alone was the cause of death in these three cases and whether the myocardial lesions found at necropsy were sequelae of the injury or resulted from natural disease requires careful analysis of the circumstances of the injury as well as of the clinical features. Naturally, the longer the interval between the injury and death the greater the difficulties. Nevertheless it may be of crucial medicolegal importance to know the answer to these questions.

The aetiology of a diffuse myocardial fibrosis found at necropsy is difficult to determine. The myocardium reacts to various harmful effects in much the same way. According to Simpson (1967), primary myocardial lesions such as those caused by hypertension, coronary insufficiency, and viral, bacterial, spirochetal, fungal, protozoal, or trypanosomal infection may cause fibrosis. Simpson thought that diffuse fibrosis represented the end stage of different primary myocardial lesions. The damage to the heart may be so extensive that one wonders how it managed to function (Burch, Tsui, and

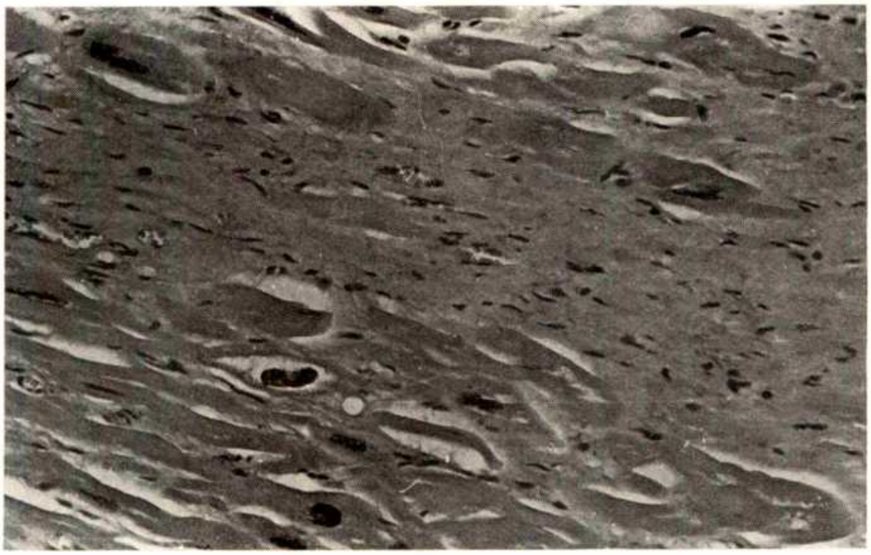

FIG. 4 *Case 3. Photomicrograph showing left ventricular wall. Area of dense collagenous connective tissue separates muscle fibres, which lie singly or in small groups. Enlarged hyperchromatic nuclei indicate myocardial hypertrophy. (Haematoxylin-eosin.* × *100.)*

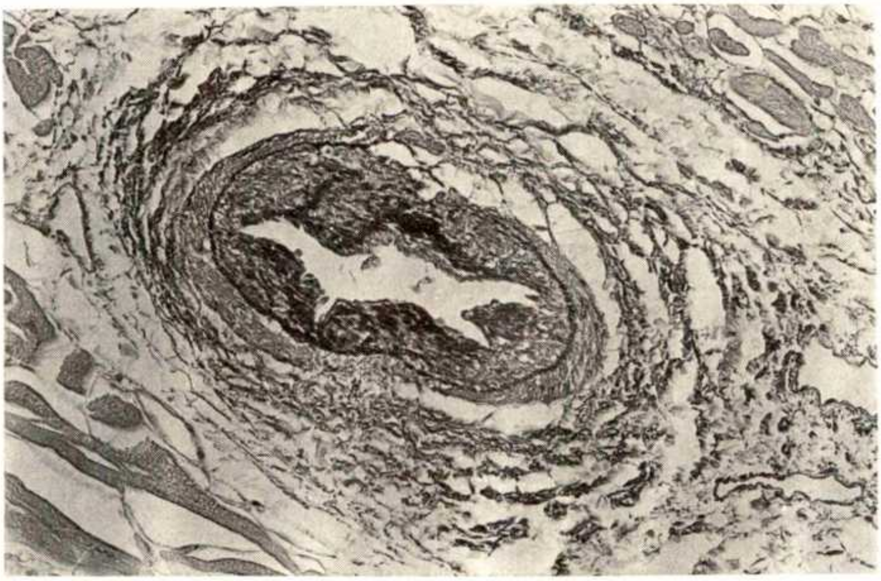

FIG. 5 *Case 3. Photomicrograph showing thickening of arterial wall and increase in perivascular connective tissue. (Weigert's resorcin fuchsin elastic stain.* × *100.)*

Harb, 1972). Myocardial lesions are known to develop secondary to craniocerebral injury. Aschenbrenner and Bodechtel (1938) reported electrocardiographic abnormalities in young patients with brain tumours. Other reports followed of abnormalities in the electrocardiogram associated with intracranial processes and craniocerebral injury in man and with similar electrocardiographic changes experimentally induced in animals (Burch, Meyers, and Abildskov, 1954; Burch, DePasquale, and Malaret, 1960; Shkhvatsabaya, 1961; Eichbaum and Bissetti, 1966; Plueckhahn and Cameron, 1968; Burch *et al.*, 1969; Reichenbach and Benditt, 1970; Anderson, Woodburn, and Fisch, 1973; Cruickshank, Neil-Dwyer, and Stott, 1974).

Plueckhahn and Cameron (1968) differentiated a type of myocarditis that was a direct or indirect complication of trauma and which resulted from systemic hypoxia. They termed it 'traumatic myocarditis', and they reported it in 3 cases of craniocerebral injury associated with unconsciousness. Eichbaum and Bissetti (1966) assumed the pathogenesis of encephalogenic lesions of the heart to be as follows. All forms of surgical and traumatic stress stimulate sympathetic centres in the hypothalamus. This stimulation is particularly strong if the intracranial pressure increases, especially if the increase is sudden. Catecholamines are released and the resulting increased cathecholamine concentrations cause myocardial lesions and cardiovascular disturbances.

Catecholamines such as noradrenaline or isoprenaline given to experimental animals induce similar myocardial lesions (Eichbaum and Bissetti, 1966). Garbarsch *et al.* (1969) noted degenerative and necrotic changes in the arterial wall of rabbits after systemic oxygen deprivation for two weeks. In the processes of repair fibrosis and sclerosis similar to human arteriosclerosis develop. According to these workers similar changes in the arterial wall can be induced by the administration of exogenous catecholamines.

There are few reports on prognosis in cases of recent encephalogenic myocardial lesions. Plueckhahn and Cameron (1968) believed that infiltration with round cells or leucocytes may occur at later stages, and pointed out that this type of myocardial lesion might produce only transient clinical symptoms. Shkhvatsabaya (1961) and Shkhvatsabaya and Postnov (1967) induced changes in the electrocardiogram and myocardial necrosis and formation of granulation tissue in rabbits with cerebral stimulation by blowing air into the lateral ventricles of the brain.

According to Connor (1970) fuchsinophilic degeneration and focal myocytolysis in advanced stages are usually irreversible but they may occasionally 'heal', provided that the lesions are not too extensive and fibrosis develops. Reichenbach and Benditt (1970) believed that catecholamines might induce acute myocardial lesions in man as well as in experimental animals, and if these lesions are sufficiently extensive they can contribute to, or be the cause of, death. Repeated episodes of subarachnoid haemorrhage may result in condensation of the stroma of the heart muscle, fibrosis, and cardiac failure. These workers emphasized that more attention should be paid to these lesions when considering the causes of human cardiac disease.

The myocardial lesions in our three cases illustrate different stages in the development of encephalogenic myocardial lesions (Table). A study of the published reports suggests that Case 1 was similar to that reported by Plueckhahn and Cameron (1968) with respect to the clinical and pathological findings. This also applied to Case 2, though an additional pathological finding was stromal condensation which, according to Reichenbach and Benditt (1970), represents a more advanced myocardial lesion than that in Case 1. Case 3 showed myocardial fibrosis resembling what Simpson (1967) termed the end stage of a primary non-specific myocardial lesion. Vascular changes in the form of fibrosis and thickening of the wall in small arterial branches, in the absence of signs of necrosis and inflammation of the vessel wall, were also morphologically non-specific in type. They recall the reparative and sclerotic changes that Garbarsch *et al.* (1969) identified in rabbits after oxygen deprivation as well as the postmortem findings in children described by Pesonen (1974) in cases of hypoxaemia. Pesonen suggested that these vascular lesions occurred either simultaneously with the myocardial lesions or preceded the latter—that is, hypoxic myocardial lesions are sequelae of vascular changes.

We may reasonably assume that the severe trauma to the skull and the development of myocardial fibrosis in Case 3 were related, for the following reasons. 1) The patient had a history of severe craniocerebral injury associated with unconsciousness. 2) There was nothing to show that he might have had cardiac disease before his accident. The measles and scarlatina later might have played a part in the subsequent development of cardiac lesions. However, he was followed up after his accident at regular intervals for 7 years; he never showed any signs or symptoms of cardiac disease. 3) The myocardial fibrosis was morphologically non-specific in character.

The lesions in small arterial branches as well as the myocardial lesions may have arisen in conjunction with craniocerebral injury and may have been involved in the development of chronic ischaemic cardiac disease (cardiomyopathy), with a gradual increase of myocardial fibrosis resulting in heart failure and death. This may occur without causing any preceding symptoms.

Reports suggest that it is not only craniocerebral injury that can trigger the process in the myocardium but also intracranial disease causing an increase in intracranial pressure.

Conclusions

Acute lesions of the myocardium after craniocerebral injury are recognized increasingly and are much discussed. These lesions may give rise to fibrosis of the myocardium, resulting in cardiac insufficiency and death. In cases in which the past history includes craniocerebral injury associated with unconsciousness, and myocardial fibrosis and cardiac insufficiency are present, a relation between the latter lesions and the previous cerebral trauma should be considered.

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Vigorous exercise in leisure time, coronary risk-factors, and resting electrocardiogram in middle-aged male civil servants

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During 1968 to 1970, approximately 17 000 middle-aged male executive grade civil service officers, all of them engaged in sedentary or very light work, recorded on a Monday morning their leisure time activities over the previous Friday and Saturday. In 1971 a sample of 509 of these men completed further questionnaires for medical, social, and smoking history; these men had a resting electrocardiogram, and height, weight, skinfold thickness, blood pressure, and plasma total cholesterol were measured. Vigorous exercise in leisure time had previously been reported by 125 (25%) of the men, and these as a group had significantly fewer electrocardiographic abnormalities (changes compatible with myocardial ischaemia, ectopic beats, and sinus tachycardia) than the men not reporting vigorous exercise ($P<0{\cdot}02$). This difference remained when all men with any history suggestive of cardiovascular disease were excluded from the analysis. Blood pressure, plasma total cholesterol, and smoking habits were examined with respect both to vigorous exercise and to the electrocardiogram, but the only relation found was that electrocardiographic abnormality increased with increasing blood pressure. Even among men with higher pressures, however, those reporting vigorous exercise had fewer electrocardiographic abnormalities than the others. The results provide further support for the association of habitual physical activity with coronary health.

Many studies have associated increased physical activity with a reduction in subsequent coronary morbidity and mortality (Morris *et al.*, 1953; Fox and Haskell, 1968; Brunner *et al.*, 1974; Paffenbarger and Hale, 1975), but few have examined its relation to electrocardiographic evidence of subclinical myocardial ischaemia. In Finland, Karvonen *et al.* (1961) found fewer abnormal electrocardiograms among lumberjacks than among men in other occupations. Keys *et al.* (1966) also reported less evidence of myocardial ischaemia in men with physically demanding work than in those in sedentary occupations. In Italy, railroad workers and men in rural districts, groups in which about 30 per cent and 65 per cent of men respectively were judged to be in heavy physical work, showed less electrocardiographic ischaemia than male clerks (Menotti *et al.*, 1969). However, these authors were reluctant to conclude that there was a definite association between occupational physical activity and coronary health because they were unable to exclude the possibility that other factors relevant for coronary heart disease also differed between the groups contrasted.

In 1968 to 1970, Morris *et al.* (1973) recorded the leisure time activities of nearly 17 000 male executive grade civil servants in the U.K. Men reporting vigorous exercise in leisure time had a smaller risk of subsequent coronary morbidity and mortality than their more sedentary colleagues. This study has now been extended in order to examine the relation between vigorous exercise, other recognized coronary risk factors, and electrocardiographic evidence of myocardial ischaemia within a group of men of similar occupational and socioeconomic

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status. The results provide further evidence for an inverse association between habitual physical activity and myocardial ischaemia.

Subjects and methods

The group from which the present men were drawn comprised 16 882 male executive grade civil servants aged 40 to 65 years in six government departments in Britain. All were employed at sedentary or physically very light work. Between 1968 and 1970, each completed on an unannounced Monday morning a diary detailing activities during each five minutes of the previous Friday and Saturday (48 hours). No information was sought on activities during working hours. Questions were also asked about social, economic, and familial circumstances and on general medical history.

The method of analysis of the activity questionnaire has been given previously (Morris *et al.*, 1973). Briefly, 'vigorous exercise' was defined as any activity likely to require a peak energy expenditure of 31·5 kJ min^{-1} (7·5 kcal min^{-1}) and which, in the case of specified recreations, had lasted at least 5 minutes, and in the case of 'heavy work' had been performed either for more than 30 minutes continuously or for a total of one hour over the two-day period. Thus the men were divided into two exercise groups, those reporting vigorous exercise in leisure time and those not so reporting.

In 1971 a sample of 660 men was drawn from the original population and asked to collaborate in further studies. Of these, 509 agreed, giving a response rate of 77 per cent. Each completed a questionnaire for cardiovascular disease and answered the London School of Hygiene questionnaire for angina pectoris, prolonged chest pain, and intermittent claudication (Rose and Blackburn, 1968). Smoking habits were noted.

Height and weight were recorded and skinfold thickness was measured at three sites, subscapular, triceps, and supra-iliac, with Harpenden calipers. Casual blood pressure was recorded with the subject seated using a random zero sphygmomanometer (Hawksley). Two electrocardiograms were recorded at paper speeds of 2·5 and 5·0 cm s^{-1}, respectively. Venous blood was withdrawn for plasma total cholesterol concentration measured by 'Autoanalyser' using a modified Lieberman-Burchard method (Stitt *et al.*, 1973).

All electrocardiograms were read independently by two observers according to Minnesota code criteria (Blackburn *et al.*, 1960) and discrepancies were submitted to an arbitrator. Major Q wave changes (Minnesota code 1–1, 2) were classified as definite myocardial ischaemia and lesser Q wave changes (1–3), ST segment depression (4–1, 2, 3), T wave inversion without evidence of left ventricular hypertrophy (5–1, 2), and complete bundle-branch block (7–1, 2) were taken as evidence for possible myocardial ischaemia. Subsequently, a third observer recorded the amplitude of the tallest R wave in left praecordial leads (V5–V6), the duration of the PR interval in lead II, the occurrence of any premature beat, and the resting heart rate. All readings of the electrocardiograms and classification of activities were done independently and without any other information about the subjects. Frequency of electrocardiographic abnormality was then compared between the two exercise groups.

Results

Vigorous exercise as defined was reported by 125 of the 509 men (24·6%). Table 1 shows that as a group those reporting vigorous exercise were similar to those not reporting vigorous exercise with respect to age, height, weight, and skinfold thickness. Table 2 presents plasma total cholesterol and blood pressure according to exercise group; none of the differences achieved statistical significance though a smaller proportion of men reporting vigorous exercise had a plasma total cholesterol concentration above 6·4 mmol l^{-1} (249 mg/100 ml) compared with men not reporting vigorous exercise, and a slightly greater proportion of men in the vigorous exercise group had a systolic and diastolic blood pressure above 150 mmHg (20 kPa) and 90 mmHg (12·0 kPa) respectively (more detailed analysis of the higher ranges revealed nothing of interest). There were fewer non-smokers in the vigorous exercise group than in the no vigorous exercise group, and figures for current cigarette smoking were as low as 26 per cent and 32 per cent respectively (Table 3).

Table 4 gives the resting electrocardiographic findings. In all, 11 per cent of men reporting vigorous exercise had one or more noteworthy electrocardiographic abnormality compared with 22 per cent of men not reporting vigorous exercise

TABLE 1 *Age and physique according to exercise group*

	*Reporting vigorous exercise**		*Not reporting vigorous exercise*	
	N=*125*		*N*=*384*	
Mean age (yr)	50·7	(5·7)	50·6	(5·2)
% aged 40 to 49	41·6		37·3	
% aged 50 to 59	48·0		54·4	
% aged 60 to 65	10·4		8·3	
Mean height (m)	1·740	(0·068)	1·739	(0·062)
Mean weight (kg)	74·8	(9·2)	73·9	(10·0)
Mean skinfold thickness (mm)				
Triceps	9·3	(3·4)	9·6	(3·7)
Subscapular	17·6	(6·2)	17·3	(6·0)
Suprailiac	25·1	(7·8)	24·9	(7·8)

*See 'Methods' and Morris *et al.* (1973).
Figures in parentheses are standard deviations about the mean.
None of these differences was statistically significant ($P>0·05$).

($P<0{\cdot}02$). Prominent Q waves (1–1, 2) were not found in any of the men reporting vigorous exercise while they occurred in 3 per cent of men not reporting vigorous exercise ($P<0{\cdot}05$). Similarly, the prevalence of possible myocardial ischaemia (except complete bundle-branch block); of ectopic beats; and of sinus tachycardia (Morris *et al.*, 1966; Berkson *et al.*, 1970), were all less in the vigorous exercise group than in the no vigorous exercise group.

Neither the R wave amplitude in left praecordial leads nor the duration of the PR interval in lead II appeared to be related to a history of vigorous exercise in leisure time. Thus the mean R wave amplitude was 17·1 mm (SD 5·3) and 16·7 mm (SD 5·3) in the vigorous exercise group and no vigorous exercise group, respectively. An R wave amplitude of more than 26 mm occurred in 4 (3·8%) men reporting vigorous exercise and 7 (1·8 per cent) men not reporting vigorous exercise ($P>0{\cdot}05$). The mean PR interval was 0·16s (SD 0·02) in both groups and the mean heart rate was 75 min^{-1} (SD 15) and 76 min^{-1} (SD 15) for the vigorous exercise and no vigorous exercise group, respectively.

Table 5 relates the electrocardiographic findings to blood pressure, plasma total cholesterol, and smoking habits in the two exercise groups. Irrespective of exercise category, there was no trend to increasing electrocardiographic abnormality with increasing plasma total cholesterol. In both exercise groups the prevalence of electrocardiographic abnormality did increase with increasing blood pressure, but remained lower among men reporting vigorous exercise than in men not reporting vigorous exercise, even at hypertensive levels. Cigarette smoking was not associated with any excess of electrocardiographic abnormality in either exercise group.

In 118 men the questionnaire responses indicated either definite or possible cardiovascular disease (history of myocardial infarction, angina or prolonged chest pain, hypertension, cerebrovascular accident, intermittent claudication, exertional dyspnoea) or related disorder such as diabetes mellitus. They comprised 23 per cent of both exercise groups (29 of the 125 men reporting vigorous exercise and 89 of the 384 men not reporting vigorous exercise). Exclusion of these men from the analysis left the findings essentially unchanged; thus all types of electrocardiographic abnormality listed in Table 4 remained less prevalent among men reporting vigorous exercise. After age standardization on the remaining 391 men, 9 (9·4%) of 96 men reporting vigorous exercise had one or more electrocardiographic abnormalities, as compared with 55 (18·6%) of the remaining 295 men not reporting vigorous exercise ($P<0{\cdot}05$). Ectopic beats were found in 1 (1·8%) of the men reporting vigorous exercise and 15 (5·5%) of the men not reporting vigorous exercise ($P>0{\cdot}05$).

Of the 118 men with clinical and/or 'questionnaire' evidence of cardiovascular disease, 65 gave a history of treatment for hypertension or diabetes mellitus or clinical coronary disease. Numbers are

TABLE 2 *Plasma total cholesterol and casual arterial blood pressure according to exercise group*

	*Reporting vigorous exercise**		*Not reporting vigorous exercise*	
	N=125		*N=384*	
Plasma total cholesterol (mmol/l)				
Mean	6·23	(1·01)	6·25	(1·01)
% below 5·7	30		31	
% 5·7 to 6·4	37		29	
% above 6·4	34		41	
Casual arterial pressure (mmHg)				
Mean systolic	141	(20)	137	(20)
% below 130	33		36	
% 130 to 149	31		40	
% above 149	36		24	
Mean diastolic	88	(12)	86	(11)
% below 80	27		34	
% 80 to 89	39		35	
% above 89	35		31	

*See 'Methods' and Morris *et al.* (1973).
Figures in parentheses are standard deviations about the mean
None of the differences achieved statistical significance ($P>0{\cdot}05$).
Conversion factor from SI units to Traditional Units:
cholesterol: mmol/l≈38·7 mg/100 ml
Conversion from Traditional Units to SI Units: 1 mmHg ≈0·133 kPa.

TABLE 3 *Smoking habits, according to exercise group*

Smoking habits	*Reporting vigorous exercise*	*Not reporting vigorous exercise*
	N=125	*N=384*
% Never smoked	15	20
% Pipe/cigar only	18	18
% Ex-cigarette smokers	41	31
Current cigarette smokers	26	32

None of these differences is statistically significant ($P>0{\cdot}05$).

TABLE 4 *Subjects with electrocardiographic changes, according to exercise group*

Electrocardiographic reading	*Minnesota code*	*Reporting vigorous exercise**	*Not reporting vigorous exercise*
		125 men	*384 men*
Definite and possible myocardial ischaemia		6 (4·8)	40 (10·4)†
One or more ectopic beats¶		3 (2·2)	27 (7·1)†
Sinus tachycardia	8–7	7 (5·6)	34 (8·7)
Men with any of the above observations		14 (11·1)	83 (22·1)‡
Definite ischaemia			
Major Q/QS patterns	1–1, 2	0	11
Possible ischaemia			
Minor Q/QS patterns	1–3	1	5
ST segment depression	4–1, 2, 3	3	23
T wave inversion	5–1, 2	0	9
Complete bundle-branch block	7–1, 2	2	5
Supraventricular ectopic beats		1	10
Ventricular ectopic beats		2	17
Ectopic beats comprising 10 per cent or more of recorded cycles	8–1	1	14

*Vigorous exercise as defined in 'Methods' and Morris *et al.* (1973).

†$P<0·05$; ‡$P<0·02$. When numbers are small, the significance of differences between groups was tested by the method of Gart (1962).

¶Within age range 55 to 64 years: 2 (4·8%) of 42 men reporting vigorous exercise; 11 (10·3%) of 107 men not reporting vigorous exercise.

Figures in parentheses are age-standardized rates. There were, in all, 6 instances of definite or possible ischaemic changes in 6 men who reported vigorous exercise, and 53 instances in 40 men who did not report vigorous exercise.

TABLE 5 *Prevalence of electrocardiographic abnormalities* in relation to plasma total cholesterol, casual blood pressure, smoking habits, and vigorous exercise in leisure time*

	Men reporting vigorous exercise		*Men not reporting vigorous exercise*	
	Total No.	*% with ECG abnormalities*	*Total No.*	*% with ECG abnormalities*
Plasma total cholesterol (mmol/l)				
below 5·7	37	13·5	117	23·9
5·7–6·4	46	13·0	107	16·8
above 6·4	42	7·1	160	23·1
Systolic blood pressure (mmHg)†				
below 130	41	4·9	137	13·9
130–149	39	7·7	154	20·8
above 149	44	20·5	91	34·1
Diastolic blood pressure (mmHg)†				
below 80	34	8·8	130	15·4
80–89	44	6·8	134	21·6
above 89	46	17·4	118	28·0
Smoking habits				
Never smoked	18	22·2	76	25·0
Pipe/cigar only	23	13·0	68	28·0
Ex-smokers‡	52	5·8	117	15·4
Current smokers‡	32	12·5	123	22·0

*As in Table 4.

†Not recorded in one subject reporting vigorous exercise and two subjects not reporting vigorous exercise.

‡Cigarettes with or without other types of tobacco smoking.

Conversion from SI Units to Traditional Units: Cholesterol: 1 mmol/l ≈ 38·6 mg/100 ml. 1 mmHg ≈ 0·133kPa.

now very small, but in this group of 65 men, 3 (15·8%) of the 19 reporting vigorous exercise had one or more changes of definite or possible ischaemia compared with 17 (37·0%) of the 46 not reporting vigorous exercise. The figures for ectopic beats were 1 (5·3%) and 7 (15·2%) respectively. Of the 53 men with 'questionnaire' evidence alone, 10 men not reporting vigorous exercise had electrocardiographic abnormalities, compared with none of those reporting vigorous exercise.

Discussion

In any epidemiological study which compares coronary morbidity and mortality in groups with differing habitual physical activity, due allowance must be made for the possible effects of other socioeconomic factors which might differ between the groups (Morris, 1975). In order to minimize these unwanted effects, the present study was confined to middle-aged men who were all government employees with uniform occupations and socioeconomic status ('white collar', and within a narrow band of the middle class). The two exercise groups were remarkably alike over a wide range of social indices (Morris *et al.*, 1973), and the similarity of skinfold thickness and plasma total chlesterol in the two groups may be some indication of the success of this technique. Keys *et al.* (1966) found that skinfold thickness, blood pressure, and serum cholesterol levels were inversely related to occupational physical activity, but that these apparent effects of physical activity were much reduced when some allowance was made for associated differences in socioeconomic status. The differences in the electrocardiogram in the present study between the two exercise groups are thought to be unlikely to be a consequence of other socioeconomic variables related to the pattern of physical activity.

An alternative interpretation of these data could be that the men with electrocardiographic abnormality tended to avoid leisure activity for health reasons related to ischaemic heart disease. Both Menotti *et al.* (1969) and Paffenbarger and Hale (1975) concluded from their own extensive data that this type of behavioural change must be very uncommon before the onset of *clinical* disease. In the present study, no excess of subjects with either symptoms or a clinical history of possible cardiovascular disease was, in fact, found among those not reporting vigorous exercise. And the findings remained essentially unchanged when these men were excluded from the analysis. There seemed, therefore, little likelihood that men with electrocardiographic changes had, at least one year before the electrocardiographic examination in 1971 (the activity questionnaire had been completed at some time between 1968 and 1970), changed their pattern of leisure activity for reasons related to coronary disease. More probably, the findings indicated that physical activity in some way promoted coronary health. Thus, they confirm the earlier finding (Morris *et al.*, 1973) of a reduced subsequent incidence of clinical coronary heart disease in the vigorous exercise group as compared with the no vigorous exercise group.

An increase in ectopic beats in physically inactive men has not apparently been reported previously. Karvonen *et al.* (1961) found similar rates of arrhythmia in lumberjacks and in men in less physically demanding occupations. While ectopic beats have many causes, impairment of the coronary circulation with inadequate oxygen delivery might predispose to arrhythmias (Watanabe and Dreifus, 1968; Samuelsson, 1973). Since men not reporting vigorous exercise also had more electrocardiographic changes compatible with myocardial ischaemia, their excess of ectopic beats could have been a result of ischaemic heart disease.

The protective action of vigorous exercise did not appear to be related to plasma total cholesterol, casual blood pressure, adiposity, or smoking habits. In other studies examining the relation between plasma total cholesterol and habitual physical activity, the results have been inconsistent (Keys *et al.*, 1966; Menotti *et al.*, 1969; Grimby *et al.*, 1971; Taylor, Buskirk, and Remington, 1973; Brunner *et al.*, 1974). This does not exclude the possibility that consistent group differences existed in the distribution of total cholesterol between the several plasma lipoproteins. Increased physical activity increases high density lipoprotein cholesterol while reducing low density lipoprotein cholesterol (Lopez-S *et al.*, 1974; Wood *et al.*, 1974), and on this account might improve coronary health (Miller and Miller, 1975; Lewis *et al.*, 1974; Gulbrandsen, Rhodes, and Kagan, 1974; Morris, 1975) even when plasma total cholesterol shows little change.

The absence of any increase in resting electrocardiographic abnormality with either cigarette smoking or increased plasma cholesterol is in agreement with earlier studies. Neither Epstein *et al.* (1965) nor Keys *et al.* (1966) showed any significant relation between these factors and electrocardiographic abnormalities when these included ST segment depression and T wave inversion. Indeed, as in the present study, Epstein *et al.* (1965) found fewer changes in smokers than in non-smokers. Since both cigarette smoking and a raised plasma total cholesterol are associated with an increased coronary mortality (Simborg, 1969), the meaning of these findings is unclear. Some men who were at risk for these reasons might have been excluded from the study population by earlier death. Cigarette smoking may be more strongly associated with the acute coronary event than the development of atherosclerosis (Gordon, Kannel, and McGee, 1974). The observations on plasma total cholesterol might be clarified when electrocardiographic changes are examined with respect to the plasma lipoproteins rather than plasma total cholesterol, and during exercise rather than at rest. Thus both Motta *et al.* (1974) and Carlson, Ekelund, and Olsson (1975) found that ischaemic ST segment depression during exercise occurred more frequently in subjects with hyperlipidaemia than in normal subjects. Many studies, on the other hand, have confirmed the association between electrocardiographic abnormality and blood pressure (Epstein *et al.*, 1965; Keys *et al.*, 1966; Miall *et al.*, 1972), and it is interesting (Table 5) to note the protective effect of vigorous exercise in the presence of a raised blood pressure (Morris, 1975).

While numbers are very small, the protective effect of exercise in hypertension appeared to explain much of the reduction in frequency of electrocardiographic abnormalities in those men reporting vigorous exercise within the group of 118 men who had clinical or questionnaire evidence of cardiovascular disease. There was also some evidence that effort symptoms (chest pain, dyspnoea, claudication) were less likely to be associated with electrocardiographic abnormality in men reporting vigorous exercise than in those who did not take vigorous exercise.

Heavy occupational and athletic activities are associated with an increased R wave amplitude, sinus bradycardia, and a prolonged PR interval (Karvonen *et al.*, 1961; Keys *et al.*, 1966; Van Ganse *et al.*, 1970). None of these changes was evident among men reporting vigorous exercise, and this observation suggests that the patterns of recreational activity which promote coronary health are not necessarily as vigorous as those associated with athleticism.

Further studies of this nature will be improved by the application of more sensitive and more specific methods of measurement of myocardial ischaemia and habitual physical activity. The study of Carlson *et al.* (1975), for example, illustrates the usefulness of exercise electrocardiography in epidemiology. Appropriate assessment of 'physical fitness', using the cardiovascular response to test exercise (Cotes, 1972), may prove a more useful even though indirect measure of habitual physical activity for survey purposes than questionnaire methods (Gyntelberg, 1974). Examination of the relations between these measurements within each of a range of socioeconomic groups may take us a step further in our understanding of the association between the pattern of habitual physical activity and coronary health.

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Sinoatrial disease in acute myocardial infarction[1]
Long-term prognosis

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Of 32 patients with acute myocardial infarction complicated by sinoatrial disease, 23 survived. All 23 had inferior infarction. During follow-up lasting 4 to 6 years only one patient developed severe chronic sinoatrial disease (sick sinus syndrome) necessitating permanent pacemaker treatment; twelve others died during this time. In 2 of them death was sudden 5 and 6 months after infarction. Atrial pacing studies in 7 of the 11 patients still alive showed no gross abnormalities. A review of 71 patients with chronic sinoatrial disease treated with a permanent pacemaker revealed only 5 with previous documented infarction.

The present data suggest that sinus node dysfunction in patients surviving acute infarction is most often only temporary as is atrioventricular block. Occasionally, however, severe chronic sinoatrial disease requiring a permanent pacemaker may develop later, and this course of events is most likely to occur in those patients who had additional complications during the acute infarct.

The incidence and course of sinoatrial disease complicating acute myocardial infarction have been reported (Rokseth and Hatle, 1971), but the long-term prognosis is not well known. Ferrer (1973) recommends that patients who have inadequacy of the sinoatrial node during acute myocardial infarction but whose nodal function recovers should be carefully followed up indefinitely. A more chronic stage probably the result of slow fibrosis may take several months or even years to become permanent and cause syncopal episodes. Meltzer and Cohen (1972) described 4 patients all of whom showed persistent obvious sinus bradycardia or prolonged episodes of sinus arrest several months after infarction: permanent pacing was required in each case. To our knowledge no systematic studies regarding the natural course have been reported. The purpose of the present paper is to report the follow-up of patients with myocardial infarction and sinoatrial disease who were seen in the acute stage between 1966 and 1970 and previously described by Rokseth and Hatle (1971).

Patients and methods

Among the 32 patients previously described all except one had inferior infarction. Nine died during their stay in hospital. The remaining 23 patients were followed up from 4 to 6 years. There were 4 women and 19 men whose ages ranged from 40 to 82 years (mean 66). All had inferior infarction. The sinoatrial disorder was in no case related to drugs such as morphine, lignocaine, digitalis, etc. The main manifestations of sinoatrial disease during infarction were second degree sinoatrial block (intermittent cycles of twice the normal cycle length) in 7, second degree sinoatrial block of Wenckebach's type in 2, sinus arrest (here defined as a pause longer than twice the normal cycle length interrupted by an ectopic beat, excluding pauses following blocked atrial premature conduction) in 9, and slow nodal rhythm (rate 50 or less) in 5 patients. Often more than one type of sinus node dysfunction was recorded on the electrocardiogram in the same patient. Table 1 shows the total number of arrhythmias in the 23 patients. The most frequent complicating arrhythmia was atrial fibrillation which occurred in 11 patients. Atrioventricular block was seen in 8 patients and ventricular fibrillation in 1. Thirteen patients were treated with an intravenous drip of isoprenaline as occasional intravenous administration of atropine (0·5 mg) was inadequate. In 2 of them temporary pacemakers had to be used because of repeated syncope. The remaining 10 patients received no specific treatment.

On discharge 20 patients had regular sinus rhythm (rates 60 to 84) and atrial fibrillation persisted in one only. Second degree sinoatrial block of Wenckebach's type was present in 2 patients. In one of them it was later established that this rhythm had been present several

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TABLE 1 *Arrhythmias occurring while in hospital (23 patients)*

	No.
Sinoatrial block	13
Sinus arrest	9
Slow nodal rhythm	13
Atrioventricular block	8
Atrial fibrillation	11
Ventricular premature beats	2
Ventricular fibrillation	1

Note: In addition, 9 patients had periods of sinus bradycardia.

years before myocardial infarction. None had congestive heart failure on discharge but the heart size was enlarged in 10 of 19 where a chest *x*-ray was obtained.

Follow-up was usually carried out at intervals of 3 to 6 months and included clinical examination and electrocardiogram. In 7 patients electrophysiological studies were possible 4 to 6 years after infarction. All were men aged 61 to 71 years. The procedure was as follows. A bipolar electrode catheter was passed percutaneously through a femoral vein in 6 patients (cubital vein in the 7th) to the right atrium. Before atrial pacing a His bundle electrogram was obtained in the 6 patients where the femoral approach was possible. The catheter tip was placed against the lateral wall of the atrium and atrial pacing was performed by a Medtronic 5837 pulse generator at the following rates successively: 100, 110, 120, 130, and 140. The pacing time was 60 seconds at intervals of 60 seconds. Three patients then received atropine intravenously, 0·025 mg per kg body weight. The pacing procedure was repeated 5 to 15 minutes after atropine. Two patients received digoxin 0·125 mg twice daily. In Case 6, digoxin was discontinued 24 hours before investigation, and in Case 7 it was discontinued only on the morning of the investigation because of recent signs of congestive heart failure.

Sinus node recovery time (SRT) was measured from the beginning of the last spike of stimulation to the beginning of the first P wave after turning off the pacemaker. The corrected sinus recovery time was obtained by subtracting the average PP interval before pacing from sinus node recovery time. The recovery time as a percentage of the average cycle length before pacing was also calculated.

TABLE 2 *Electrocardiogram at follow-up*

	No. of patients	
	Later dead	*Alive*
Sinus rhythm	9	9
Sinoatrial block Wenckebach	1	1
Atrial fibrillation		1
Bradycardia/tachycardia	1*	
Electrocardiogram not recorded (no symptoms)	1	

*Treated with pacemaker. See text.

Clinical results at follow-up

During observation 12 patients died, 5 after 5 to 12 months, 2 after 2 years, 1 after 3 years, and 4 after 4 to 6 years. Eleven patients are still alive.

One patient developed a persistent bradytachycardia syndrome and was treated with a permanent pacemaker. Two other patients suffered rare attacks of supraventricular tachycardia. They received digoxin without known episodes of bradycardia. Angina pectoris in 4 patients was never shown to be associated with bradycardia. Recurrent infarction in 3 others was not complicated by rhythm disturbances. One patient with persistent atrial fibrillation suffered a stroke attributed to cerebral embolism. Repeat clinical examination and electrocardiogram showed a ventricular rate of 60 to 80. No patients had dizziness or syncope.

Table 2 shows the electrocardiogram at follow-up examinations. Among patients who died during the period of observation one had second degree sinoatrial block (Wenckebach) which had been present before myocardial infarction occurred, and one patient had bradycardia alternating with tachycardia. Nine patients were in normal sinus rhythm while the 12th patient died before the first control and an electrocardiogram was not recorded. Among the 11 patients still alive 9 had normal sinus rhythm.

The causes of death were cancer in 3, heart failure in 2, car accident in 1, and recurrent infarction in 1 patient. Two died of unknown causes after 2 and 5 years. Two others died suddenly at home after 5 and 6 months, respectively. No necropsy was made and the cause of death is unknown. Both had been examined during the preceding months and the electrocardiogram showed normal sinus rhythm. A third patient also died suddenly and because he was the only one who developed chronic sinoatrial disease his case history is given in some detail. He was a man aged 67. The hospital course during acute infarction had been stormy, with sinus arrest complicated by ventricular fibrillation, third degree atrioventricular block, and repeated syncope. A temporary pacemaker had to be used for 21 days. He was discharged with normal sinus rhythm (rate 68), dyspnoea on exertion, and moderate cardiomegaly. On examination 1 and 2 months afterwards his condition was unchanged. After 2 months he suffered repeated attacks of atrial tachycardia with 2:1 atrioventricular block alternating with sinus bradycardia (rate 30). His dyspnoea became worse and he was treated with a permanent pacemaker combined with digoxin 0·25 mg twice daily. No further attacks of tachycardia were recognized except during the first

TABLE 3 *Atrial pacing studies 4 to 6 years after infarction*

		Case No.						
		1	*2*	*3*	*4*	*5*	*6*	*7*
Age (y)		64	70	71	65	75	61	65
Heart rate/min		60	67	50–70*	57	73	58	84
Atrial pacing	Rate	100	120	140	140	100	140	140
	Sinus node recovery time (ms)	1200	1200	1100	1430	1050	1575	1245
	Sinus node recovery time (%)	120	130	110	140	120	150	173
	Corrected sinus node recovery time (ms)	190	300	100	380	200	540	530
		Effects of atropine						
Heart rate/min				92	80			96
Atrial pacing	Rate			120	120			140
	Sinus node recovery time (ms)			750	900			1060
	Sinus node recovery time (%)			110	120			165
	Corrected sinus node recovery time (ms)			100	150			440

*Sinus arrhythmia.

pacemaker replacement after 2 years when the electrocardiogram showed atrial tachycardia with 2:1 atrioventricular block. His condition otherwise improved. After 4 years the electrocardiogram showed atrial fibrillation, with a ventricular rate varying between 35 and 60 and complete dissociation between the pacemaker stimuli and QRS caused by lead fracture. The breakage was repaired when a second pacemaker was installed and he remained well until death occurred suddenly 5 years after infarction. The pacemaker functioned normally. Necropsy showed extensive old myocardial infarction in the anterior and inferior wall, significant arteriosclerosis in the left coronary artery, and total arteriosclerotic occlusion of the right coronary artery. Unfortunately, a description of the sinus node with its artery was not obtained.

Electrophysiological investigations

The results of atrial pacing are seen in Table 3. Basal heart rate varied from 57 to 84. One other patient had sinus arrhythmia. The pacing rate giving maximal sinus node recovery time and maximal corrected sinus node recovery time varied from 100 to 140. Maximal sinus node recovery time was 150 per cent or above and maximal corrected sinus node recovery time was above 500 ms in cases 6 and 7, both receiving digoxin before the examination. At the time of investigation we were not aware that atropine was useful when studying sinus node function. However, heart rate increased in all three patients who received atropine, the increase being only slight in case 7. Maximal corrected sinus node recovery and sinus node recovery time did not change significantly after atropine. In all experiments sinus rhythm developed after cessation of pacing and no prolonged secondary pause was observed. Atrioventricular conduction times were normal in all patients (the one whose His bundle electrogram was not obtained had a normal PQ time).

Comments

The mortality among the present 23 patients was 52 per cent, 4 to 6 years after discharge from hospital as a result of acute inferior myocardial infarction complicated by sinoatrial disease. The figure was not significantly different from the mortality in the same period (45%) among 587 patients with inferior infarction but without this complication. The average age in the two groups was similar (66 years). Only one of the 23 patients developed severe chronic sinoatrial disease or sick sinus syndrome (Lown, 1967; Ferrer, 1968) requiring permanent pacemaker treatment. Two other patients had second degree sinoatrial block of Wenckebach's type during the whole time in hospital for acute myocardial infarction and during the follow-up period. Some aetiology other than coronary artery disease could be involved. In one of them the rhythm disturbance had been recorded years before infarction. Both were free of symptoms. A fourth patient developed atrial fibrillation which persisted from the acute stage of infarction throughout the follow-up period. According to James (1961) and Ferrer (1974) atrial fibrillation could be a result of sinus node damage. We do not know if this was the case in our patient as no attempt at electroconversion has been made. This procedure might have resulted in sinus arrest if atrial fibrillation was the result of sinus node damage. In the remaining patients there were no symptoms or signs of sinoatrial disease. Sinus arrest cannot be excluded in the two patients who died suddenly. However, sudden death from other arrhythmias, e.g. ventricular fibrillation, is not an uncommon event in patients with coronary artery disease.

The electrophysiological studies showed possible slight sinus dysfunction in 2 of 7 among 11 patients who were alive after 4 to 6 years: these were the only two who received digoxin before the investigation. The role of digitalis is difficult to assess. According to clinical experience sinoatrial disorders may develop during digitalis intoxication. But there was no suspicion of digitalis intoxication in our patients. Unpublished studies in our laboratory with ouabain intravenously have occasionally shown a prolongation of sinus node recovery time though Engel and Schaal (1973) showed a statistically significant reduction of sinus node recovery time after ouabain in patients with the sick sinus syndrome. Both our patients had a sinus node recovery time of 150 per cent or more. The other patients had values of 130 and 140 per cent, respectively. It is questionable whether these latter figures are pathological as there is no general agreement on normal limits. According to Ferrer (1974), the upper normal limit is 120 to 128 per cent depending on the basal heart rate. Narula, Samet, and Javier (1972) report a normal range from 115 to 159 per cent, with the longest corrected sinus node recovery time of 525 ms. Opinions also vary regarding the atropine response. Ferrer (1973) suggests that the heart rate should normally increase above 90 while Mandel, Laks, and Obayashi (1975) suggest that the increase should be above 50 per cent, with a transitional zone between 25 and 50 per cent. Gupta *et al.* (1974) accept heart rate responses above 30 per cent as normal. Dighton (1975) found that the heart rate response after atropine was a less reliable test. Before drawing conclusions from the electrophysiological studies one must be aware that no known test of sinoatrial function is wholly reliable. Nevertheless, our results do not indicate gross abnormalities.

In order to throw further light on the course of disease we have reviewed all patients, including those referred from other hospitals, receiving permenent pacemakers from 1966 to February 1975 because of severe chronic sick sinus syndrome. Among 71 patients, 5 had previous documented myocardial infarction. All 5 developed severe sick sinus syndrome several months to one year after inferior infarction. In addition to the one already described, 2 others had sinus arrest, 1 had sinoatrial block, and 1 had prolonged sinus bradycardia during the acute stage. All had signs of extensive infarction with additional complications, such as congestive heart failure and/or prolonged hypotension. One of them had had a pulse rate of about 40 for 20 years after diphtheria and in two others electrocardiograms recorded before infarction had shown sinus bradycardia (rates 50 to 55). Nevertheless, myocardial infarction could be responsible, at least partly, for the severe chronic stage in these patients.

In order to obtain additional information on the natural course of sinoatrial disease especially during the first weeks and months after infarction serial measurements of sinus recovery time might be useful. This opportunity occurred when a bus driver aged 57 suffered acute inferior myocardial infarction in 1973. About an hour after the first symptoms he had a short bout of atrial fibrillation. Second degree 2:1 sinoatrial block developed 20 hours later, lasted a few hours, and never recurred. The course was otherwise uncomplicated, and because of his occupation specially careful follow-up was considered necessary. In addition to frequent clinical examinations atrial pacing studies were made 10 days as well as 3 and 5 and 14 months after infarction. The results are shown in Table 4. After 10 days maximal corrected sinus node recovery time was 450 ms and sinus node recovery time 150 per cent. After 3 months the corrected rate was 300 and the recovery time 130. After 5 and 14 months both figures were within limits accepted by all authors as normal.

The present material is drawn from a department with a yearly admittance of around 400 patients with acute myocardial infarction. Because sinoatrial disease is a fairly rare complication the examined group is not very large, but to our knowledge no systematic follow-up study in a larger group of patients has been reported. With this reservation our previous study (Rokseth and Hatle, 1971) and the present data suggest the following natural

TABLE 4 *Repeat atrial pacing studies after infarction*

Months after infarction		⅓	3	5½	14½
Heart rate/min		70	60	60	55
Atrial pacing	Rate	110	120	120	120
	Sinus node recovery time (ms)	1305	1300	1200	1390
	Sinus node recovery time (%)	150	130	120	125
	Corrected sinus node recovery time (ms)	450	300	200	300

course in patients with myocardial infarction complicated by sinoatrial disease. Inferior infarction is almost always present. Signs of sinoatrial disease often occur early, during the 3 first days after onset of chest pain, and are mostly of short duration, hours to a few days, and do usually not recur during hospital stay. Electrophysiological investigation may, however, unmask sinus node dysfunction for some time afterwards. Occasionally, sinoatrial disease may be a malignant complication lasting for weeks during acute infarction and requiring temporary pacemaker. If death occurs it is generally from other causes, such as shock and congestive heart failure. In survivors the long-term outlook as regards sinus node function is generally good. But chronic severe sick sinus syndrome requiring a permanent pacemaker may occasionally later develop especially in patients with a severe course and additional complications during acute infarction. These patients should, therefore, be carefully followed at least for a year. It should be borne in mind that sudden death may conceivably be caused by undetected sinoatrial disease, and it remains to be shown if repeat electrophysiological investigations may detect latent sinus node dysfunction preceding a severe development.

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Electrocardiographic antecedents of primary ventricular fibrillation

Value of the R-on-T phenomenon in myocardial infarction[1]

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Primary ventricular fibrillation was seen in 20 of 450 consecutive patients (4·4%) admitted within 24 hours after the onset of acute myocardial infarction. Compared with patients without primary ventricular fibrillation, they showed a lower mean age group and a higher incidence of anterior infarction. Warning ventricular arrhythmias preceded primary ventricular fibrillation in 58 per cent of cases. However, warning arrhythmias were also present in 55 per cent of patients without primary ventricular fibrillation. The following mechanisms of initiation of primary ventricular fibrillation were seen. 1) In one patient, it was initiated by supraventricular premature beats showing aberrant intraventricular conduction. 2) In 2 patients, ventricular tachycardia degenerated into primary ventricular fibrillation. 3) In 17 patients, it was initiated by a ventricular premature beat; in 10 of these, the premature beat showed early coupling (RR′/QT<1—the R-on-T phenomenon). However, ventricular premature beats showing the R-on-T phenomenon were also observed in 49 per cent of patients without primary ventricular fibrillation. In 7, primary ventricular fibrillation was initiated by a late-coupled ventricular premature beat (RR′/QT>1); in 2, the very late coupling resulted in a ventricular fusion beat. The study suggests that warning arrhythmias and the R-on-T phenomenon are poor predictors of primary ventricular fibrillation in acute myocardial infarction. The observation that 41 *per cent of primary ventricular fibrillation was initiated by a late-coupled ventricular premature beat suggests that ventricular vulnerability during acute myocardial infarction may extend throughout most of the cardiac cycle and is not necessarily confined to the QT interval.*

The concept of ventricular vulnerability was first shown in animal models by Wiggers and Wegria (1940) and Wiggers, Wegria, and Pinera (1940). Later, the clinical extrapolation of this concept was highlighted by the phrase 'R-on-T' phenomenon (Smirk, 1949; Smirk and Palmer, 1960). However, a few clinical reports (Mounsey, 1967; Stock, 1970; Lie, Wellens, and Durrer, 1974a; De Soyza *et al.*, 1974) and some recent experimental observations (Scherlag *et al.*, 1974; Williams *et al.*, 1974; El-Sherif, Scherlag, and Lazzara, 1975b) suggested that the arrhythmogenic potentials in acute myocardial ischaemia were not exclusively confined to those extrasystoles exhibiting the R-on-T phenomenon. This report examines the role of the R-on-T phenomenon in 20 cases of primary ventricular fibrillation observed at the Coronary Care Unit during a 2-year period. In addition, we analysed other electrocardiographic characteristics of primary ventricular fibrillation and their potential value as predictors of the arrhythmia. A summary of this report was recently published in abstract form (El-Sherif *et al.*, 1975a).

Subjects and methods

Studies were made on 450 consecutive patients with acute myocardial infarction admitted to the coronary care unit from November 1972 to October 1974. All patients were admitted within 24 hours of the onset of prolonged chest pain suggestive of acute myocardial

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infarction, with a mean arrival time to the coronary care unit of 4 hours. The diagnosis of acute myocardial infarction was based on all the following criteria: 1) a typical clinical history; 2) electrocardiographic abnormalities consisting of either new Q waves or typical evolutionary ST-T changes; and 3) characteristic serial changes in serum enzymes including CK, AST, and LDH. The site of old and acute infarction was determined and defined according to criteria as outlined by Lipman and Massie (1965). Primary ventricular fibrillation was defined as ventricular fibrillation in the absence of congestive failure, pulmonary oedema, and cardiogenic shock (Meltzer and Kitchell, 1966; Lawrie *et al.*, 1967).

In all patients, continuous electrocardiographic monitoring was performed, and in several patients these data were stored on a 24-hour magnetic tape-recorder using the Holter monitoring system. The first episode of primary ventricular fibrillation was always recorded and analysed for the mechanism of initiation. The heart rate immediately preceding the arrhythmia was noted. The prematurity index of the ventricular premature beat that initiated the first and subsequent episodes of primary ventricular fibrillation was determined by dividing the coupling interval of the ventricular premature beat (RR′) by the QT interval of the preceding sinus beat. In the present study, to facilitate description and analysis of the results, a ventricular premature beat with prematurity index less than 1 was considered to represent short coupling or the R-on-T phenomenon while a ventricular premature beat with an index of 1 or more was termed long coupling. The time of occurrence of the first episode of primary ventricular fibrillation after the onset of symptoms was noted. All records were analysed for the presence of warning arrhythmias defined as 1) ventricular premature beats with a frequency of more than 5 beats/min; 2) multiform ventricular premature beats; 3) ventricular premature beats in couplets; 4) premature beats falling on the T wave (R-on-T phenomenon); and 5) ventricular tachycardia (DeSanctis, Block, and Hutter, 1972). All patients showing warning arrhythmias received lignocaine infusion at a rate of 2 to 4 mg/min, with an initial bolus injection of 75 to 100 mg intravenously. Procainamide, quinidine sulphate, and phenytoin were given as second choice antiarrhythmic drugs in several patients. None of these drugs was given before the onset of primary ventricular fibrillation, except for one patient in whom the initiating arrhythmia was supraventricular premature beats.

Results

Age, sex, site of infarction, and outcome (Table 1)

Of 450 patients with acute myocardial infarction, 20 developed primary ventricular fibrillation (4·4%). The mean age of these patients was 55 years, being lower than the mean age of 63 years of those patients without primary ventricular fibrillation ($P < 0{\cdot}05$). The incidence of fibrillation was slightly greater in patients with anterior myocardial infarction (12 of 221 patients) than in patients with inferior infarction (8 of 179 patients) ($P < 0{\cdot}1$).

TABLE 1 *Age and sex distribution, site of infarct, and outcome*

	Primary ventricular fibrillation	*No primary ventricular fibrillation*
Incidence	20	430
Mean age (y)	55	63
Sex:		
Male	16	335
Female	4	95
Site of infarct:		
Anterior	12	221
Inferior	8	179
In-hospital mortality	2	65

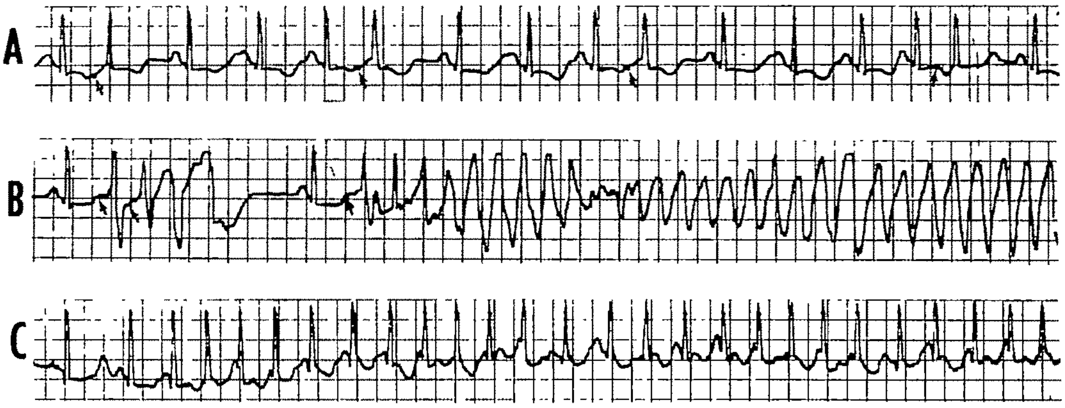

FIG. 1 *Primary ventricular fibrillation initiated by supraventricular premature beats (marked by arrows). See text for details.*

Eight patients were receiving lignocaine. All patients were successfully resuscitated. The in-hospital mortality of 450 patients with acute myocardial infarction was 15 per cent. Of 20 patients with primary ventricular fibrillation, 6 had recurrent episodes (up to 12). One patient died from cardiogenic shock 24 hours after repeated defibrillation. Another patient died on the fifth hospital day from reinfarction and cardiogenic shock. All 18 patients who were successfully cardioverted left the hospital and were still alive for a follow-up period ranging from 3 to 24 months.

Mode of onset of primary ventricular fibrillation

Three different patterns of initiation were observed.

1) In a unique example of a 54-year-old man, the fibrillation was initiated by supraventricular premature beats (Fig. 1). The patient was admitted within two hours from the onset of acute anterior myocardial infarction. The rhythm strip showed frequent supraventricular premature beats, some with short coupling conducted with a slight degree of aberrant intraventricular conduction (Fig. 1, panel A, marked with arrows). The patient was started on oral quinidine, 0·4 g every 6 hours. However, 2 hours after admission, the frequency of supraventricular premature beats was not diminished and, furthermore, the ectopic beats conducted with a high degree of aberrant intraventricular conduction. The first part of panel B of (Fig. 1) shows two supraventricular premature beats conducted with wide QRS followed by two other bizarre ventricular beats before the self-termination of the arrhythmic episode. The second episode in panel B started with an early-coupled supraventricular premature beat which was aberrantly conducted and followed by the onset of ventricular fibrillation. It is difficult to exclude the possibility that more than one supraventricular premature beat was conducted with aberration as in the first episode, before triggering ventricular fibrillation. The patient was successfully defibrillated and started on lignocaine, but continued for the next two hours to show recurrent bouts of ventricular fibrillation initiated by exactly the same mechanism as shown in panel B. After repeated defibrillation, the patient's rhythm changed to atrial fibrillation with rapid ventricular response (Fig. 1, panel C), before reverting spontaneously to sinus rhythm, 8 hours after the onset of symptoms. Analysis of the patient's corrected QT interval showed that it was only moderately prolonged (0·44–0·48 s). Serum potassium and calcium were within normal limits. Review of the patient's previous and follow-up electrocardiograms failed to show any evidence of a pre-excitation syndrome.
2) In 2 patients, a regular ventricular tachycardia for 15 and 40 minutes, respectively, degenerated into primary ventricular fibrillation. The tachycardia was resistant to lignocaine therapy and, in one patient, it failed to respond to cardioversion. In both patients, a predominantly regular tachycardia became irregular; several very early coupled ventricular ectopic beats with different QRS configuration were observed shortly before one of these beats initiated the primary ventricular fibrillation (Fig. 2).
3) In 17 patients, primary ventricular fibrillation was initiated by a ventricular premature beat during sinus rhythm or a high degree AV block. Table 2 shows the prematurity index of the ventricular premature beat that initiated ventricular fibrillation in the 17 patients. In 10 patients, the prematurity index was < 1 (short coupling on R-on-T phenomenon) (Fig. 3). Seven patients had a prematurity index of >1 (long coupling). In two patients, the ventricular premature beat that initiated ventricular fibrillation was inscribed so late in the cardiac cycle that it fell after the next P wave, resulting in a ventricular fusion beat (Fig. 4). Panel A shows frequent ventricular premature beats pre-

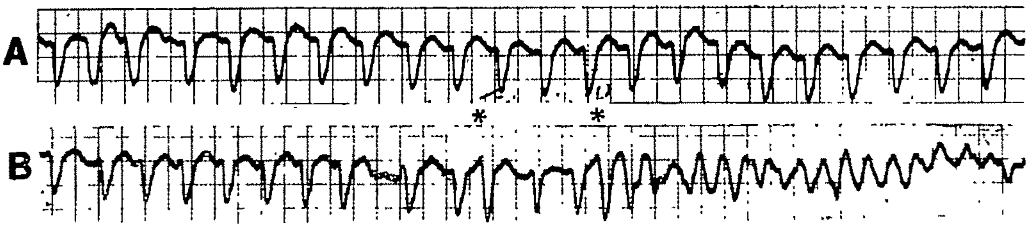

FIG. 2 *Primary ventricular fibrillation initiated by very early coupled ventricular premature beat (marked by asterisk) during course of regular ventricular tachycardia.*

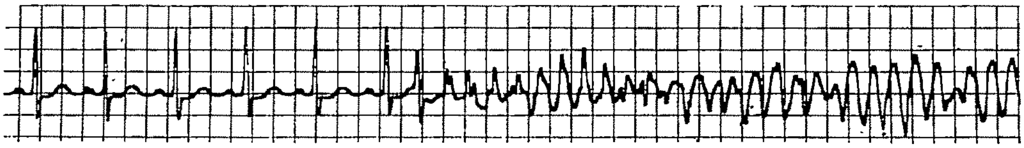

FIG. 3 *Primary ventricular fibrillation initiated by early coupled ventricular premature beat falling on antecedent T wave (R-on-T phenomenon).*

TABLE 2 *Prematurity index of ventricular premature beat initiating first episode of primary ventricular fibrillation in 17 patients (coupling interval RR′ divided by QT duration)*

Case No.	*RR′**	QT*	*Prematurity index*
1	28	40	0·70
2	36	44	0·82
3	38	52	0·73
4	46	48	0·96
5	42	56	0·75
6	38	44	0·86
7	42	50	0·84
8	30	36	0·83
9	40	60	0·67
10	32	40	0·80
11	46	38	1·21
12	50	48	1·04
13	62	56	1·11
14	58	42	1·38
15	60	52	1·15
16	56	44	1·27
17	140	60	2·33
Average	49·7	47·7	1·03
SD	25·5	7·5	0·40

*Times are in one-hundredths of a second.

dominantly in a bigeminal rhythm (marked by asterisks). The first ventricular premature beat has a very long coupling interval and probably represents a ventricular fusion beat. Panel B illustrates three ventricular premature beats with long coupling, showing varying degrees of ventricular fusion. The third ectopic beat initiated the episode of ventricular fibrillation. The patient was successfully defibrillated but showed recurrent bouts of ventricular fibrillation and was defibrillated 12 times.

Table 3 shows the relation between the time interval from the onset of symptoms to the occurrence of the first episode of primary ventricular fibrillation and the prematurity index of the ventricular premature beat that initiated the arrhythmia. Five out of seven episodes of ventricular fibrillation that were initiated by a ventricular premature beat with long coupling (P > 1) developed within 4 hours from the onset of symptoms. On the other hand, only 2 out of 10 episodes of ventricular fibrillation that were initiated by a ventricular premature beat with short coupling (prematurity index < 1) occurred within

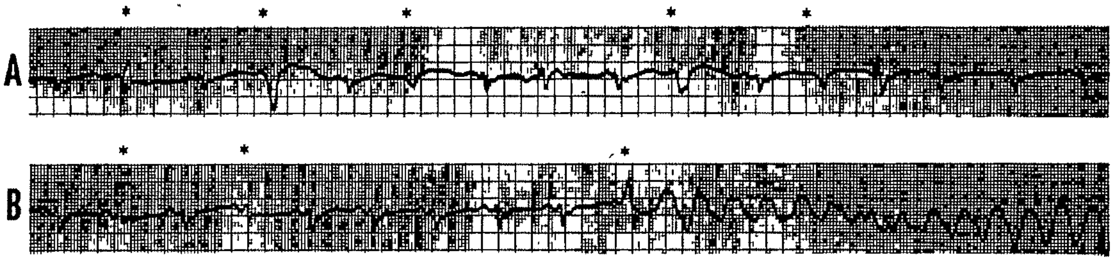

FIG. 4 *Primary ventricular fibrillation preceded by frequent ventricular premature beats (marked by asterisks) occurring predominantly in bigeminal arrangement (panel A). Panel B shows three very late coupled ventricular ectopic beats resulting in ventricular fusion complexes (marked by asterisks), third of which initiated arrhythmia.*

TABLE 3 *Relation between time of onset from start of symptoms of first episode of primary ventricular fibrillation and prematurity index of ventricular premature beat initiating arrhythmia*

Time (h)	*Prematurity index* >1	<1
0–4	5	2
4–8	1	3
8–12	1	2
12–24	—	2
>24	—	1
Total	7	10

4 hours from onset of symptoms. The difference is statistically significant ($P < 0{\cdot}05$).

The electrocardiograms obtained during the first 24 hours in hospital of 430 patients who did not develop primary ventricular fibrillation were analysed for the presence of ventricular premature beats with a prematurity index < 1. Ventricular premature beats with prematurity index < 1 showing the R-on-T phenomenon were found in 210 patients (49%). This was only slightly lower than the incidence of premature beats with prematurity index < 1 in patients who developed ventricular fibrillation (10 out of 17 patients—59%). Short coupled ventricular premature beats were observed before the onset of the arrhythmia in 5 of the 10 patients in whom fibrillation was initiated by a ventricular premature beat with prematurity index < 1. On the other hand, none of the 7 patients in whom ventricular fibrillation was initiated by a ventricular premature beat with a prematurity index < 1 showed short coupled ventricular premature beats before the onset of the arrhythmia. However, 4 of these patients started to show premature beats with prematurity index < 1 for the first time after being defibrillated, and in 2 patients subsequent episodes of ventricular fibrillation were initiated by such beats with a prematurity index less than 1.

Warning arrhythmias and heart rates preceding primary ventricular fibrillation

Warning arrhythmias preceded primary ventricular fibrillation in 11 out of 19 patients (58%) (excluding the case of ventricular fibrillation initiated by supraventricular premature beats). Eight patients showed no warning arrhythmias. These included three patients with no recognized ventricular premature beats, three with occasional premature beats with prematurity index >1, and two in whom an episode of ventricular bigeminy started 15 and 60 seconds, respectively, before one of the fixed coupled ventricular premature beats started primary ventricular fibrillation (Fig. 5). Table 4 shows the duration of monitoring before onset of ventricular fibrillation. Except for one patient who was monitored for only 30 minutes, patients who showed no warning arrhythmias were monitored for 1 to 6 hours before the onset of ventricular fibrillation. Warning arrhythmias were also present in 236 out of 430 patients (55%) who did not develop primary ventricular fibrillation. The difference between the incidence of warning arrhythmias in patients who developed or did not develop primary ventricular fibrillation was not statistically significant.

The ventricular rates immediately preceding the first episode of ventricular fibrillation are shown in

TABLE 4 *Duration of monitoring before onset of primary ventricular fibrillation*

Time (h)	*With no warning arrhythmias*	*With warning arrhythmias*
0–½	—	2
½–1	1	1
1–2	3	2
2–6	4	4
6–12	—	1
>12	—	1
Total	8	11

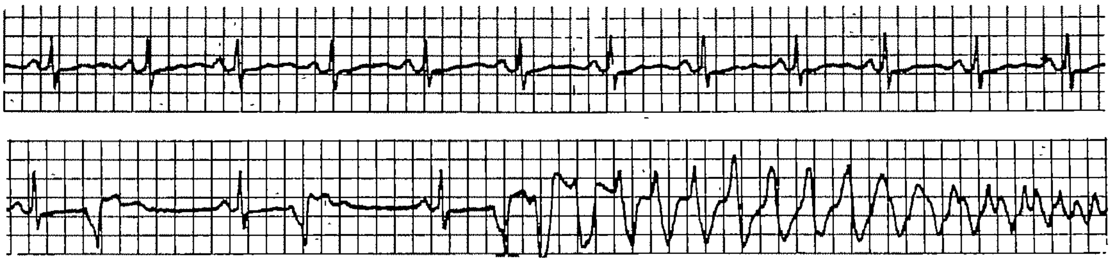

FIG. 5 *Primary ventricular fibrillation preceded by run of ventricular bigeminy for only 60 s before one of fixed coupled ventricular premature beats started arrhythmia.*

TABLE 5 *Ventricular rates immediately preceding first episode of primary ventricular fibrillation*

Heart rate (beats/min)	*No. of patients*
<40	1
40–60	2
60–80	3
80–100	6
100–120	4
120–140	1
>140*	2

*Patients with ventricular tachycardia that deteriorated into primary ventricular fibrillation.

Table 5. Three patients had heart rates less than 60/min. In 2 patients this was the result of sinus bradycardia with a rate of 40 to 60/min. The third patient had a 3:1 AV block with an atrial rate of 110/min after atropine injection. Sinus rhythm with ventricular rates of 60 to 100/min was present in 9 patients, while 5 patients showed sinus tachycardia (100 to 140/min) before ventricular fibrillation.

Discussion

The consistent demonstration of supraventricular premature beats immediately preceding the onset of ventricular tachycardia and fibrillation episodes in the patient whose electrocardiogram is illustrated in Fig. 1 strongly suggests a cause-and-effect relation. However, proof would have required reproducing the ventricular arrhythmia by induced critically timed atrial premature beats, which was obviously not feasible. This example of ventricular fibrillation initiated by supraventricular premature beats represents the first clinical report of its kind in patients with acute myocardial infarction. Ventricular fibrillation induced by supraventricular beats had been described in patients with pre-excitation (Dreifus *et al.*, 1971). One case has been recently reported in which repetitive self-terminating episodes of ventricular fibrillation were induced by supraventricular beats in a 35-year-old woman after cardiac surgery (Sakamoto, Yamada, and Hiejima, 1973): the patient had an unexplained bizarre T wave and an obviously prolonged QT interval. This is different from the present case where the QT interval was only moderately prolonged. Contrary to the obvious rarity of primary ventricular fibrillation initiated by supraventricular premature beats in patients with acute myocardial infarction, in the experimental model, properly timed supraventricular premature beats could induce ventricular fibrillation if ventricular vulnerability is altered secondary to acute ischaemia (Carrol, Ahuja, and Manning, 1965). This probably suggests that a premature beat of any sort can initiate malignant ventricular arrhythmia if it occurs sufficiently early in the presence of altered ventricular vulnerability. Our observation that supraventricular premature beats initiated episodes of primary ventricular fibrillation only when they began to show a higher degree of aberrant intraventricular conduction may suggest that the mechanism of the arrhythmia was re-entry initiated by a striking delay of activation in some part of the ventricular myocardium.

Some of the antiarrhythmic drugs used in this study may have varying effects on the QT interval and coupling intervals of ventricular premature beats. In 42 per cent of patients antiarrhythmic drugs were not given before the onset of ventricular fibrillation because of absence of warning arrhythmias. None of the remaining patients with ventricular fibrillation were given procainamide or quinidine before the onset of the arrhythmia; both drugs are known to prolong both the QT interval and coupling intervals (Giardina and Bigger, 1973). On the other hand, lignocaine seems to have little or no effect on both the QT interval and coupling intervals (Surawicz and Lasseter, 1970). This suggests that the drug regimen used during the study did not influence the observations on the prematurity index of the ventricular premature beats that initiated primary ventricular fibrillation.

An interesting observation was the limited value of warning arrhythmias in predicting the occurrence of primary ventricular fibrillation. Thus, while warning arrhythmias were present in only 58 per cent of patients who developed primary ventricular fibrillation, similar arrhythmias were also present in 55 per cent of those who did not develop fibrillation. Similar observations were previously reported (Dhurandhar, MacMillan, and Brown, 1971; Lie *et al.*, 1974a). These observations strengthen the argument for prophylactic therapy against primary ventricular fibrillation once an acute ischaemic episode is suspected without reliance on the presence or absence of warning arrhythmias. This approach could be further consolidated if the recent preliminary reports (Lie *et al.*, 1974b; Valentine *et al.*, 1974) of the efficacy of lignocaine in the prevention of ventricular fibrillation are upheld by subsequent studies. Antiarrhythmic therapy may be less effective if applied after the onset of warning arrhythmias. Similar observations have been previously reported (Dhurandhar *et al.*, 1971; Lie *et al.*, 1974a).

The most provocative finding in the present report is the reassessment of the role of the R-on-T phenomenon in primary ventricular fibrillation. In 7 out of 17 patients (41%), it was initiated by a ventricular premature beat with prematurity index >1. The demonstration that 41 per cent of fibrillation was initiated by a ventricular premature beat with long coupling (index >1) in addition to the finding that premature beats with short coupling (index < 1) were observed in 49 per cent of patients who did not develop primary ventricular fibrillation strongly suggests that the R-on-T phenomenon may be a poor predictor of malignant arrhythmias in the early phases of acute myocardial infarction. Few previous reports have shown that ventricular tachyarrhythmias in patients with acute myocardial infarction may be initiated by a ventricular premature beat that does not fall on antecedent T waves (Mounsey, 1967; Stock, 1970). In a recent systematic study (De Soyza *et al.*, 1974), the prematurity index of a ventricular premature beat was found to be a poor predictor of ventricular tachycardia during acute myocardial infarction. Assessment of the role of a ventricular premature beat that initiates an episode of ventricular fibrillation is sometimes clouded by the argument that ventricular fibrillation was not initiated by the first long coupled ventricular premature beat but rather by a subsequent beat that has a very short coupling interval. Others avoided this argument by stating that salvos of ventricular premature beats deteriorated into ventricular fibrillation (Lie *et al.*, 1974a). This argument becomes irrelevant if the first premature beat that initiates an episode of fibrillation is viewed as an integral part of an underlying pathophysiological process and represents the first electrocardiographically evident part of this process (El-Sherif *et al.*, 1975b). The data accrued from several recent studies on experimental myocardial infarction (Han, 1969; Waldo and Kaiser, 1973; Boineau and Cox, 1973; Scherlag *et al.*, 1974; Williams *et al.*, 1974; El-Sherif *et al.*, 1975b) have shed light on the mechanism of initiation of primary ventricular fibrillation in the early stages of myocardial ischaemia. Some studies (Scherlag *et al.*, 1974; Williams *et al.*, 1974; El-Sherif *et al.*, 1975b) have shown that most of the malignant ventricular tachyarrhythmias that follow shortly after ligation of a major coronary vessel are initiated by a long coupled ventricular premature beat and not by one that interrupts the antecedent T wave. This observation is explained by a characteristic pathophysiological mechanism whereby an increasing dispersion of ventricular activation results in a re-entrant tachyarrhythmia (Scherlag *et al.*, 1974; El-Sherif *et al.*, 1975b). Williams *et al.* (1974) found that after acute occlusion of a major coronary vessel in the dog, a ventricular premature beat induced so late in the cardiac cycle to result even in ventricular fusion could induce ventricular fibrillation when the underlying dispersion of ventricular activation was great. In the same study, analysis of episodes of ventricular tachycardia leading to fibrillation showed a progressive increase in the degree of dispersion of ventricular activation of successive beats, whereas in those self-terminating episodes it progressively decreased. These observations provide the pathophysiological explanation for the theoretical question of which beat actually initiated the fibrillation.

Our finding that the majority of cases of ventricular fibrillation initiated by a ventricular premature beat with long coupling seem to occur relatively early in the course of acute myocardial infarction as compared with cases of fibrillation initiated by a short coupled beat is of some interest. Several *in vivo* (Scherlag *et al.*, 1974) and *in vitro* studies (Lazzara, El-Sherif, and Scherlag, 1973; Friedman *et al.*, 1973) suggest that ventricular fibrillation occurring early and late in the course of acute myocardial infarction may have different pathophysiological mechanisms. Re-entry caused by obvious disparity of action potential durations (Lazzara *et al.*, 1973), as well as the contribution of enhanced automaticity which can trigger non-homogeneous conduction (Cranefield, 1973), are possible factors in late primary ventricular fibrillation.

Discretion is always required when data from experimental studies are extrapolated to the clinical situation. However, recent experimental studies offer a satisfactory explanation for the clinical observation that primary ventricular fibrillation can be initiated by a ventricular premature beat with long coupling while a ventricular premature beat with short coupling in other patients with acute myocardial infarction is not associated with ventricular fibrillation. Both the clinical and experimental observations call for a reassessment of both the concept of ventricular vulnerability and the R-on-T phenomenon. Though it may be true that, in the normal heart, the vulnerable phase may be limited to the QT interval, in ischaemia with obvious dispersion of ventricular activation, the vulnerable phase can extend throughout most of the cardiac cycle (Scherlag *et al.*, 1974; Williams *et al.*, 1974; El-Sherif *et al.*, 1975b). Our observations should not be construed to mean that ventricular premature beats with short coupling are not clinically significant but rather to point out that the arrhythmogenic potential in acute myocardial infarction is not confined to those extrasystoles showing the R-on-T phenomenon. Furthermore, at least in our series, the R-on-T phenomenon was a poor discriminator for the occurrence of ventricular fibrillation. This report, as well as others (De Soyza *et al.*, 1974), seems to depart from a widely held view (Lown and Wolf, 1971) that certain characteristics of the ventricular premature beat can serve as predictors of malignant ventricular arrhythmias in the early phase of acute coronary ischaemia.

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Successful electrical pacing for complete heart block complicating diphtheritic myocarditis[1]

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A case of severe diphtheria complicated by myocarditis and neurorespiratory paralysis is reported. The myocarditis manifested with severe conduction disturbances including left bundle-branch block and high-grade second degree atrioventricular block leading to Adams-Stokes attacks. Temporary transvenous electrical pacing for 3 days was successful in the management of this complication, but positive pressure ventilation was later required for respiratory paralysis. This case illustrates the potential value of electrical pacing in diphtheritic myocarditis. Sporadic cases of diphtheria still occur and the case fatality ratio remains at 10 per cent, much of which is related to the occurrence of myocarditis.

As a result of widespread immunization the incidence of diphtheria has declined dramatically during the last half century. However, even in countries with effective public health programmes outbreaks still occur and it is noteworthy that the case fatality ratio remains constant at 10 per cent (Munford *et al.*, 1974). Respiratory paralysis and myocarditis account for the majority of fatalities. The use of positive pressure ventilation has been a significant therapeutic advance but the potential

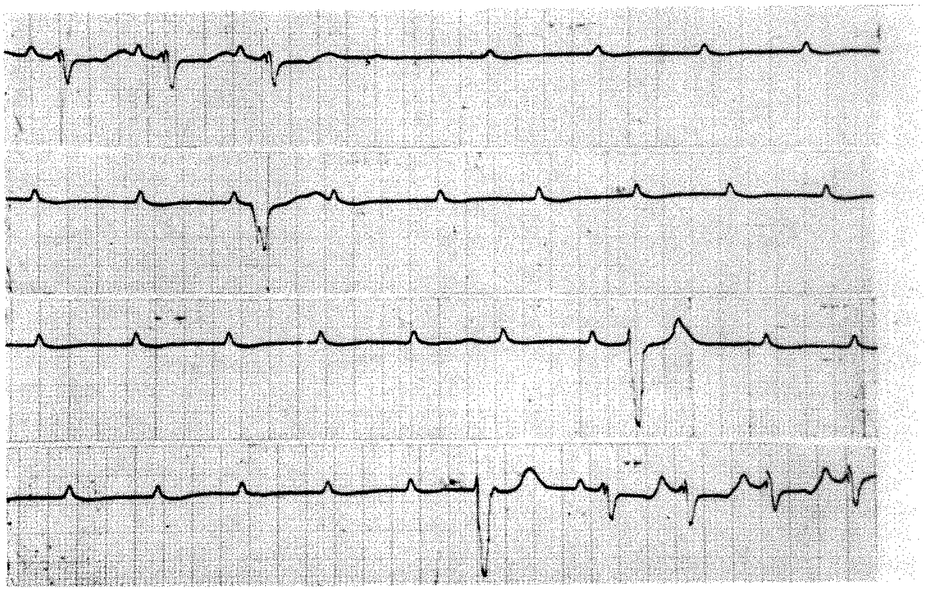

FIG. 1 *Continuous electrocardiographic monitor strip on admission showing prolonged period of asystole.*

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value of electrical pacing has not been exploited.

J. F. Goodwin (1974, personal communication) was not aware of any report on the use of electrical pacing in diphtheritic myocarditis. In this paper we report the successful use of this technique in the management of a case of severe diphtheria complicated by complete heart block and respiratory paralysis.

Case report

An 8-year-old black boy was referred from an outlying hospital where he presented with a sore throat associated with cervical lymphadenitis. The possibility of diphtheria was entertained, but because a throat swab was negative for mycobacterium diphtheria, antidiphtheritic serum was unfortunately not given. He was treated with intramuscular penicillin, with some improvement. On the tenth day, however, he had a generalized seizure from which he recovered without neurological deficit. It was then noticed that there were episodes of bradycardia and asystole and he was transferred to our hospital.

On admission he was semiconscious and in a state of shock, with cold extremities. The pulse rate was 70 beats a minute with periods of asystole and the blood pressure was 50/30 mmHg (6·7/4·0 kPa). The electrocardiogram showed high grade second degree atrioventricular block, with complete failure of atrioventricular conduction for periods of up to 8 seconds (Fig. 1). An intravenous infusion of isoprenaline restored sinus rhythm but there was a pattern of complete left bundle-branch block. A temporary pacing electrode was inserted via a superficial vein in the right antecubital fossa. A paced rate of 100 beats a minute restored the patient to full consciousness. The pacemaker was set on the demand mode and after 3 days of continuous pacing there was a reversion to sinus rhythm with a pattern of complete left bundle-branch block (Fig. 2a). On the fifth day the electrocardiogram showed a pattern compatible with left anterior hemiblock and anterior myocardial damage, with less widening of the QRS complexes (Fig. 2b). On the seventh day there was further narrowing of the QRS complexes, but the mean QRS axis remained at –60° (Fig. 2c). The temporary pacemaker was then removed and there were no further episodes of heart block.

The patient remained well for the next four weeks but then developed weakness of the legs with loss of reflexes, followed in rapid succession by vocal cord and intercostal muscle paralysis. He was transferred to the respiratory intensive care unit where a tracheostomy was performed; positive pressure ventilation was necessary for 28 days. After intensive physiotherapy he recovered completely. When discharged 3 months after admission, the electrocardiogram still showed left anterior hemiblock with a normal QRS duration.

The serum diphtheria antitoxin titre on admission was 25 units/ml, which, in an unimmunized individual who had not received antidiphtheritic serum, is regarded as diagnostic of diphtheria.

Comment

Although diphtheria is a preventable disease, sporadic cases still occur. For example, a recent analysis of diphtheria deaths in the United States for the period 1959 to 1970 (Munford *et al.*, 1974) has confirmed the overall dramatic decrease in the reported morbidity and mortality but clearly indicates that the case fatality ratio remains at 10 per cent. Several factors are concerned in the risk of dying from diphtheria. Firstly, survival is more common in patients who receive antitoxin early in the course of the disease. Secondly, strain-virulence and host factors are involved and case fatality ratios are highest in the extreme age groups, with children under the age of 5 years being particularly vulnerable. Persons who have received recommended doses of toxoid are at less risk than those who have had none. However, approximately 10 per cent of cases of diphtheria occur in persons who have been fully immunized, and the risk of mortality appears to be higher in small outbreaks, suggesting that delayed recognition with late administration of appropriate therapy is operative. It seems, therefore, that the potential for confrontation with diphtheria is always present and that unless appropriate therapeutic measures are adopted fatalities are unavoidable.

The most lethal complication of the disease is myocarditis which is a result of circulating exotoxin. Myocarditis occurs in approximately 10 per cent of cases, and Hoyne and Welford (1934) found a mortality rate of 62 per cent in their analysis of 496 cases.

Electrocardiographic changes in diphtheria have been variously reported in 16·5 to 84 per cent but most observers place the figure at 25 per cent (Wesselhoeft, 1940; Gore, 1948). The electrocardiographic abnormalities in diphtheritic myocarditis fall under two heads (Laurent, 1949). 1) Tracings showing diffuse myocardial damage with low voltage, prolongation of the QT interval, and T wave flattening or inversion are the most frequent findings. 2) Tracings showing evidence of damage to the conducting system with first, second, and third degree atrioventricular block as well as left and right bundle-branch block and left anterior hemiblock. The development of atrioventricular dissociation or complete heart block is particularly ominous and mortality rates vary from 54 to 100 per cent. Bundle-branch block carries an equally high mortality (Bigg, 1937; Burkhardt, Eggleston, and Smith, 1938; Engle, 1949).

We have not been able to find a report of successful electrical pacing in this disease. Our case suggests, however, that the chance of survival may

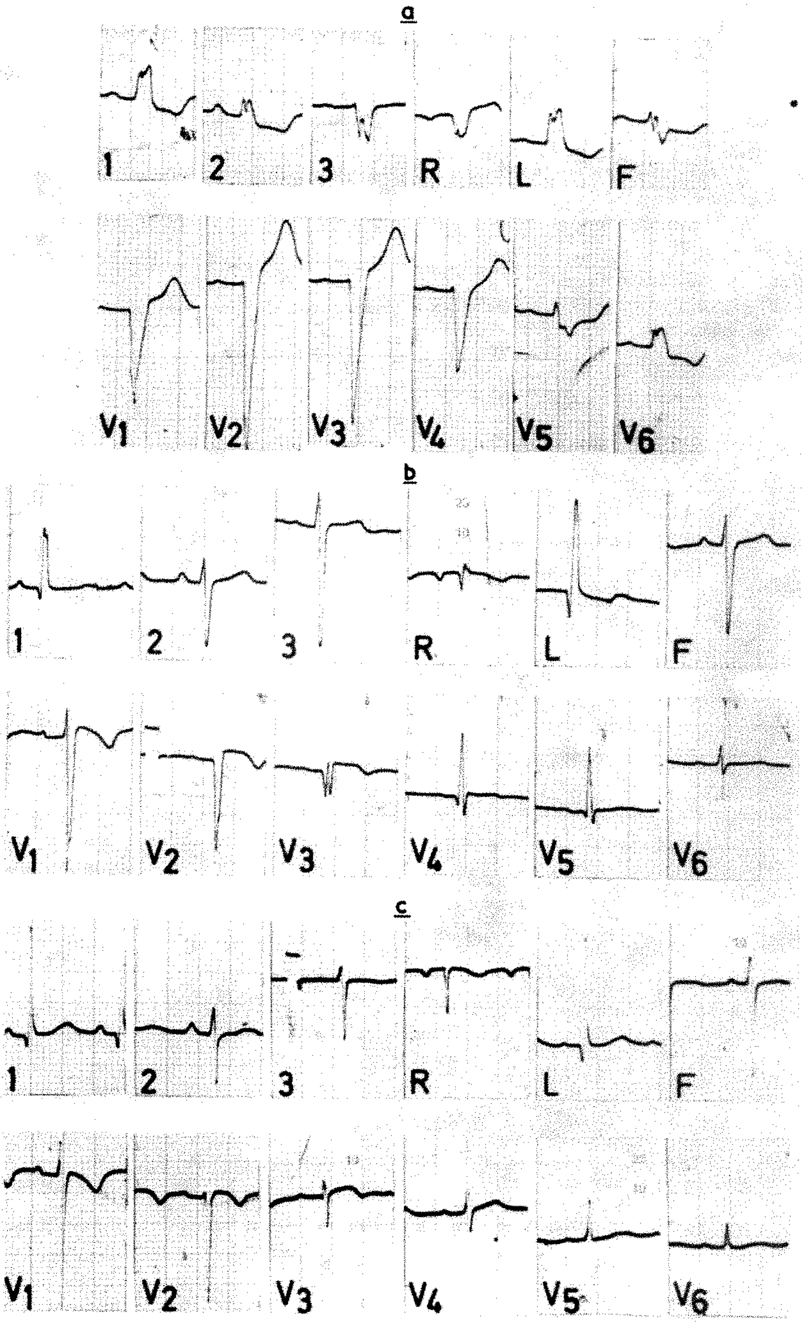

FIG. 2 *a) Electrocardiogram immediately after cessation of 3 days of continuous pacing showing sinus rhythm with complete left bundle-branch block. b) Electrocardiogram 5 days after cessation of pacing showing left anterior hemiblock and anterior myocardial damage. c) Electrocardiogram 7 days after cessation of pacing showing left anterior hemiblock and narrowing of the QRS complexes compared with a) and b) above.*

be improved with modern pacing techniques. Even in countries where diphtheria is uncommon, diagnosis of a case should lead to constant electrocardiographic monitoring and measurement of intracardiac enzymes (Chesler, 1958). Recognition of myocarditis should be followed by prompt referral to a specialized centre with facilities for monitoring, cardiac pacing, and positive pressure ventilation.

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Spontaneous variations in atrioventricular conduction in pre-excitation

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Atrial pacing in a patient with a Wolff-Parkinson-White syndrome pattern showed unusual variability in AV nodal conduction time. Changes in the AV nodal conduction time occurred predominantly at paced rates in excess of 100/min and consisted of abrupt or gradual decreases in the AH interval. Such decreases resulted in unexpected normalization of the QRS pattern. In addition, pacing also revealed evidence of block in the accessory pathway. Such changes in atrioventricular conduction may account for the known variability of the QRS pattern in patients with the WPW syndrome. Further, they may also explain the benign clinical course in this patient.

Electrical pacing in conjunction with intracardiac electrography has improved our understanding of the Wolff-Parkinson-White (WPW) syndrome (Wellens, 1975). Using these techniques the electrophysiological properties of the atrioventricular (AV) node and the accessory pathway that predispose to and perpetuate supraventricular tachyarrhythmias can be delineated. They have also helped to explain the known variability of the QRS morphology in patients with this syndrome. Delay in AV nodal conduction leads to ventricular activation predominantly through the accessory pathway, and results in an increase in the QRS deformity, whereas block in the accessory pathway results in diminution or disappearance of the delta waves and normalization of the QRS complex (Massumi and Vera, 1971). In the patient reported here normalization of the QRS pattern occurred because of an unusual mechanism—namely, an unexpected improvement in AV nodal conduction. Electrophysiological studies in this patient also showed spontaneous variations in conduction through the accessory pathway. In addition to its effects on the QRS morphology, spontaneous variability of conduction through both these pathways may also explain the absence of bouts of tachycardia.

Case report

A 28-year-old white man was admitted for the investigation of a cardiac murmur. Except for one brief episode of 'palpitations' at the age of 18, he had been asymptomatic. Cardiac examination was unremarkable except for a short, soft systolic murmur along the left sternal border. A routine electrocardiogram revealed type A WPW pattern. Cardiac catheterization and angiography showed no evidence of congenital or acquired heart disease. Because of the absence of bouts of tachycardia with the WPW pattern electrophysiological studies were performed to determine the functional characteristics of the AV nodal and the accessory pathways. Atrial pacing was carried out with a bipolar electrode catheter positioned high in the right atrium. His bundle electrograms were recorded by the technique described by Scherlag and associates (1969).

With increasing rates of atrial pacing there was a progressive increase in the AV nodal conduction time, as indicated by a prolongation of the AH intervals. Conduction through the accessory pathway contributed increasingly to ventricular activation, resulting in larger delta waves. The response to atrial pacing was thus generally similar to that reported previously (Castellanos *et al.*, 1970). However, interesting changes in the AV nodal conduction pattern occurred during pacing at rates in excess of 100/min, consisting of unexpected decreases of the AH interval ranging up to 85 ms. The reduction in the AH interval was often gradual and progressive over several cycles. Rarely, it was abrupt and confined to one or two cycles (Fig. 1A, B). The improvement in AV nodal conduction resulted in a concomitant reduction in the size of the delta waves, since ventricular activation took place predominantly through the AV node and the His bundle. Thus the QRS complexes became more normal in spite of an unchanged rate and in the absence of block in the accessory pathway.

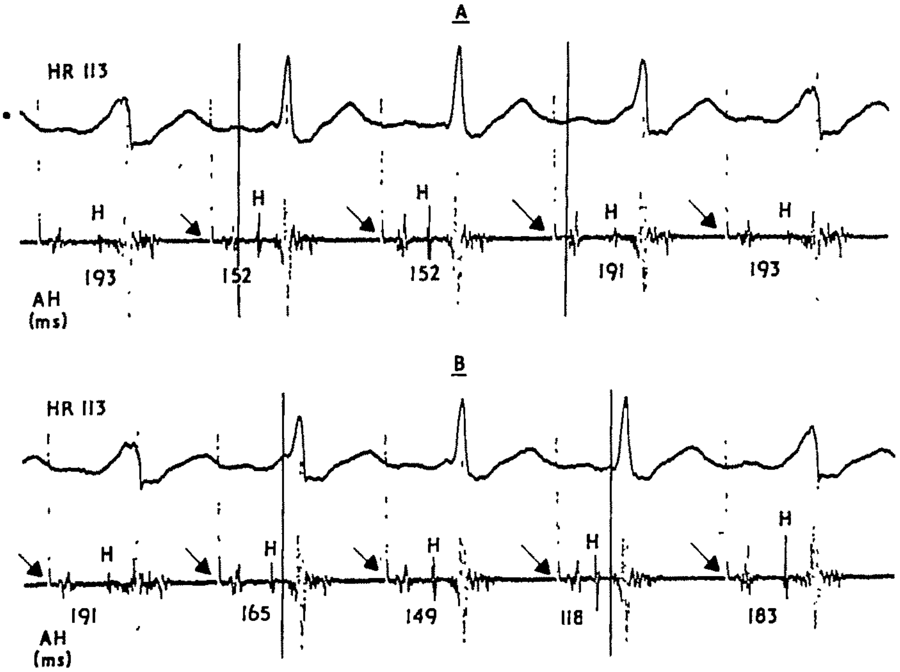

FIG. 1 *Representative records made during atrial pacing at 113/min. Arrows indicate stimulus artefacts. Note abrupt decrease in AH interval in second and third beats in panel A, and gradual decrease (second, third, and fourth beats) in panel B. In both instances improvement in AV nodal conduction results in virtual disappearance of delta wave and normalization of QRS complex (see text for discussion).*

Two additional findings suggested that spontaneous variability of conduction also occurred in the accessory pathway. The first of these was the sudden diminution in the size of the delta wave in isolated beats in the absence of any change in AV nodal conduction (Fig. 2 A), and the second was the observation that block in the accessory pathway induced by pacing was not reproducible. Fig. 2B and C shows an example of this latter phenomenon. At a paced rate of 130/min refractoriness of the accessory pathway is indicated by the disappearance of the delta waves (Fig. 2B). However, when pacing at the same rate was repeated several minutes later the accessory pathway was no longer refractory, as shown by the reappearance of large delta waves (Fig. 2C). Since these changes in the QRS pattern occurred in the absence of any change in the AH interval they must be attributed to variability of conduction in the accessory pathway.

Discussion

Of principal interest in the patient reported here is the unusual variability in AV conduction involving both the AV node and the accessory pathway. Previous reports have suggested that variability in AV nodal conduction may be the result of spontaneous changes in the autonomic tone or of functional longitudinal dissociation of the AV node into two or more pathways (Silverman and Goodman, 1951; Kistin, 1963; Langendorf, 1958). The abrupt manner in which the AH intervals decreased and the frequent presence of such a decrease in only one or two beats argue against variations in the autonomic tone being the sole mechanism in our patient. Though functional longitudinal dissociation of the AV node has been shown in patients during atrial pacing (Rosen, Mehta, and Miller, 1974), the applicability of this concept to the patient under discussion is questionable, since the wide range of AH intervals observed is unusual and would require postulation of several pathways within the AV node. A similar uncertainty exists in attempting to explain the variability of conduction in the accessory pathway. Block in the accessory pathway may occur during premature atrial stimulation and also during rapid atrial pacing (Durrer *et al.*, 1967; Castellanos *et al.*, 1970). Its occurrence in isolated beats, as shown in Fig. 2, and its lack of reproducibility are less common and suggest spontaneous variations in the refractoriness of the accessory pathway.

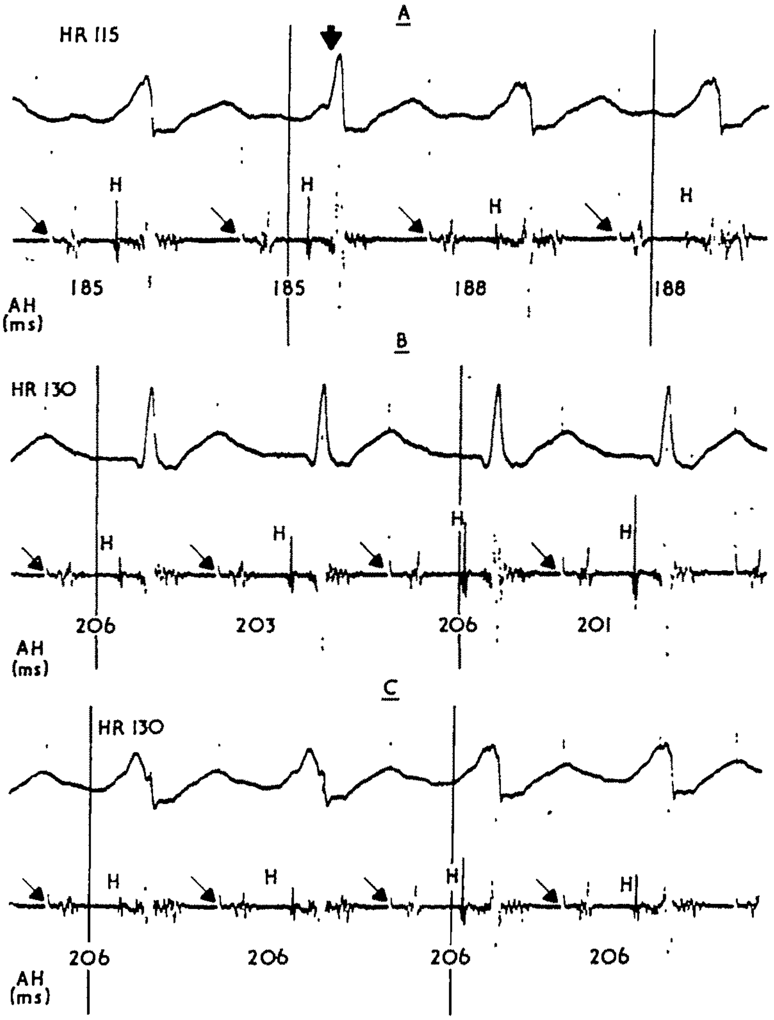

FIG. 2 *Panels A, B, and C show variability of conduction in accessory pathway. Sudden diminution in size of the delta wave (arrow, panel A) in absence of any change in AH interval indicates conduction delay in accessory pathway. Panels B and C were recorded during atrial pacing at 130/min. Note absence of delta waves in B and reappearance in C when pacing at same rate was resumed several minutes later (see text for discussion).*

Although the mechanisms underlying the variations in atrioventricular conduction are unclear, the effect of such changes is interesting in two respects. The first is its role in the normalization of the QRS complex, and the second is its possible relation to the absence of tachyarrhythmias in this patient. Normalization of the QRS complex occurs because of the development of block in the accessory pathway, but may also be seen in sinus beats terminating long pauses (Massumi and Vera, 1971). In the patient reported here it occurred as the result of an improvement in AV nodal conduction unrelated to a change in rate. The absence of tachycardias noted in this patient agrees with previous clinical observations that in a substantial proportion of patients with the WPW pattern bouts of tachycardia may be short and inconsequential or absent (Chung, Walsh, and Massie, 1965).

The reasons underlying such relative freedom from attacks of tachycardia are not clear. The findings in the patient reported here suggest a possible explanation. The initiation of tachycardia in patients with the WPW syndrome depends on a critical disparity in the refractory periods of the AV nodal and accessory pathways. Once initiated, the perpetuation of such tachycardias requires that conduction in the various components of the circuit remains reasonably constant. Significant variations in conduction, abrupt or gradual, as shown in Fig. 1 and 2, may be expected to lead to the cessation of tachycardias. It is reasonable to suggest that a similar variability in the AV nodal and accessory pathway conduction may account for the benign clinical course in other patients with the WPW pattern.

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Requests for reprints to Dr. R. Parameswaran, Albert Einstein Medical Center, York and Tabor Roads, Philadelphia, Pennsylvania 19141, U.S.A.

Correspondence

British Heart Journal, 1976, **38**, 431–432.

Electron microscopical study of myocardial biopsy material in congenital heart block

Sir,

Dr. Ludatscher and her colleagues (*British Heart Journal* (1975), **37**, 561) may, I think, have overinterpreted their electron micrographs of myocardial biopsy tissue. The number and appearance of the transverse tubules in their Case 1 (Fig. 2) are not clearly abnormal, particularly as the tissue is overcontracted as so often happens with biopsy material. In animal studies, it is not uncommon to note that the number of transverse tubules seems to vary in different cells and even in different parts of the same cell.

Secondly, the pathological significance of the deep invaginations or deep infoldings of sarcolemma must be open to some doubt. The only illustration of this (Fig. 6) shows invaginations which could well be part of the normal transverse tubular system, as seen when mammalian myocardial cells are sectioned transversely at Z-band level (Simpson, Rayns, and Ledingham, 1973, 1974).

Finally, there is the question of 'focal disruption' of myofibrils. Other authors also have used similar terminology. Alexander (1966, 1967) described myofibrils 'fragmented into short segments' in alcoholic heart disease, while Auger and Chenard (1967) described 'broken myofibrils', and Wellmann (1968) 'short and fragmented myofibrils', in beer drinkers' cardiomyopathy. Burch *et al.* (1971) described myofibrils in alcoholic mice, that were 'not continuous from one Z band to the next' so that the 'fragmented unattached myofilaments are incapable of normal contraction'. The illustrations in all these papers (including Fig. 2 of the paper by Ludatscher *et al.*) show myofibrils cut obliquely so that it is not surprising that the myofibrils pass out of the plane of section. This does not mean that they are disrupted or fragmented in the sense that they come to an end somewhere in the middle of the cell. Such fragmentation is not impossible but so far no convincing evidence for it has been put forward, so far as I am aware. Serial sections or very accurate longitudinal sections down the myofibrils would be required to show this point. The problem seems partly to be that in some types of myocardial disease the myofibrils have a less parallel orientation than usual. It is not yet clear what this means in terms of attachment of the ends of the myofibrils.

F. O. Simpson,
Wellcome Medical Research Institute,
Department of Medicine,
University of Otago Medical School,
Dunedin,
New Zealand.

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This letter was shown to Dr. Ludatscher who replies as follows:

I agree that variation in the number of transverse tubules should be considered. However, in numerous thin sections examined from Case 1 the number of T-tubules was impressive in comparison with descriptions of myocardium from patients with cardiomyopathy (Van Noorden, Olsen, and Pearse, 1971; Ferrans, Morrow, and Roberts, 1972), and with necropsy material from different heart conditions available in our laboratory.

In Case 2, Dr. Simpson's comments are correct in that the sarcolemmal invaginations could well be part of the transverse tubular system. I opted for 'deep invaginations of the sarcolemma with formation of intracytoplasmic channels', because these channels were not present in the interior of the cell or at the Z-band level though they were of unusual length. As for the focal disruption of myofilaments in areas occupied by clusters of mitochondria, there is no way of proving that disruption had actually occurred. Nevertheless, myofibrillar disorientation and disruption are known to occur in pathological conditions of the heart (Ferrans *et al.*, 1972).

Ruth Ludatscher,
Technion School of Medicine,
Haifa, Israel.

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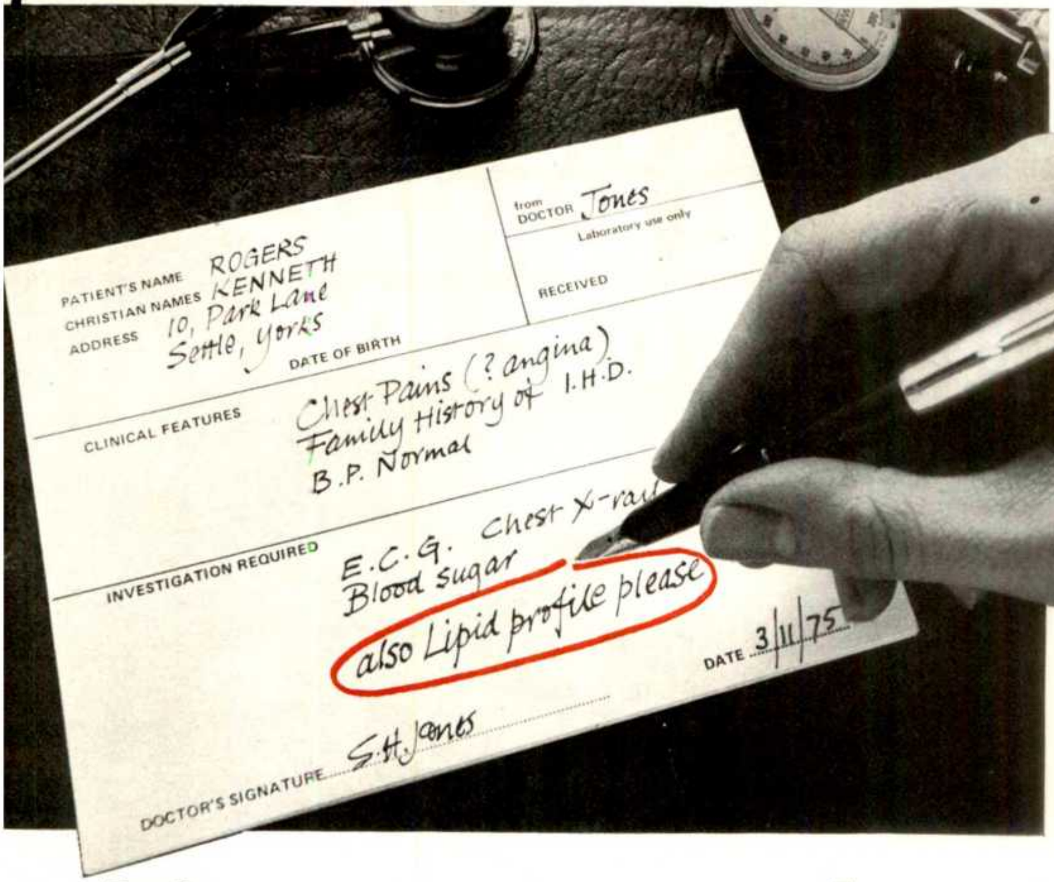

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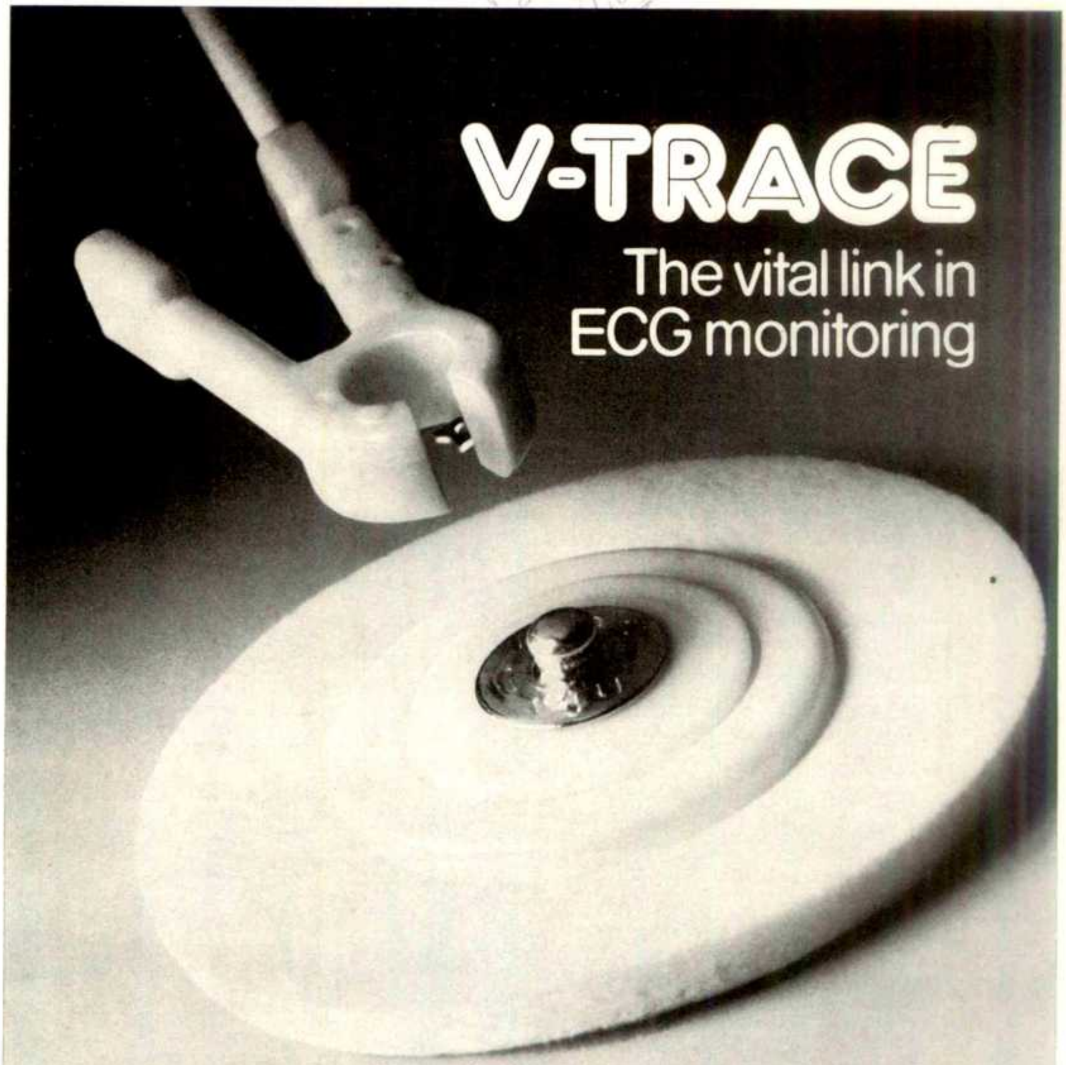

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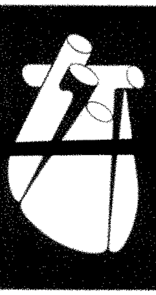

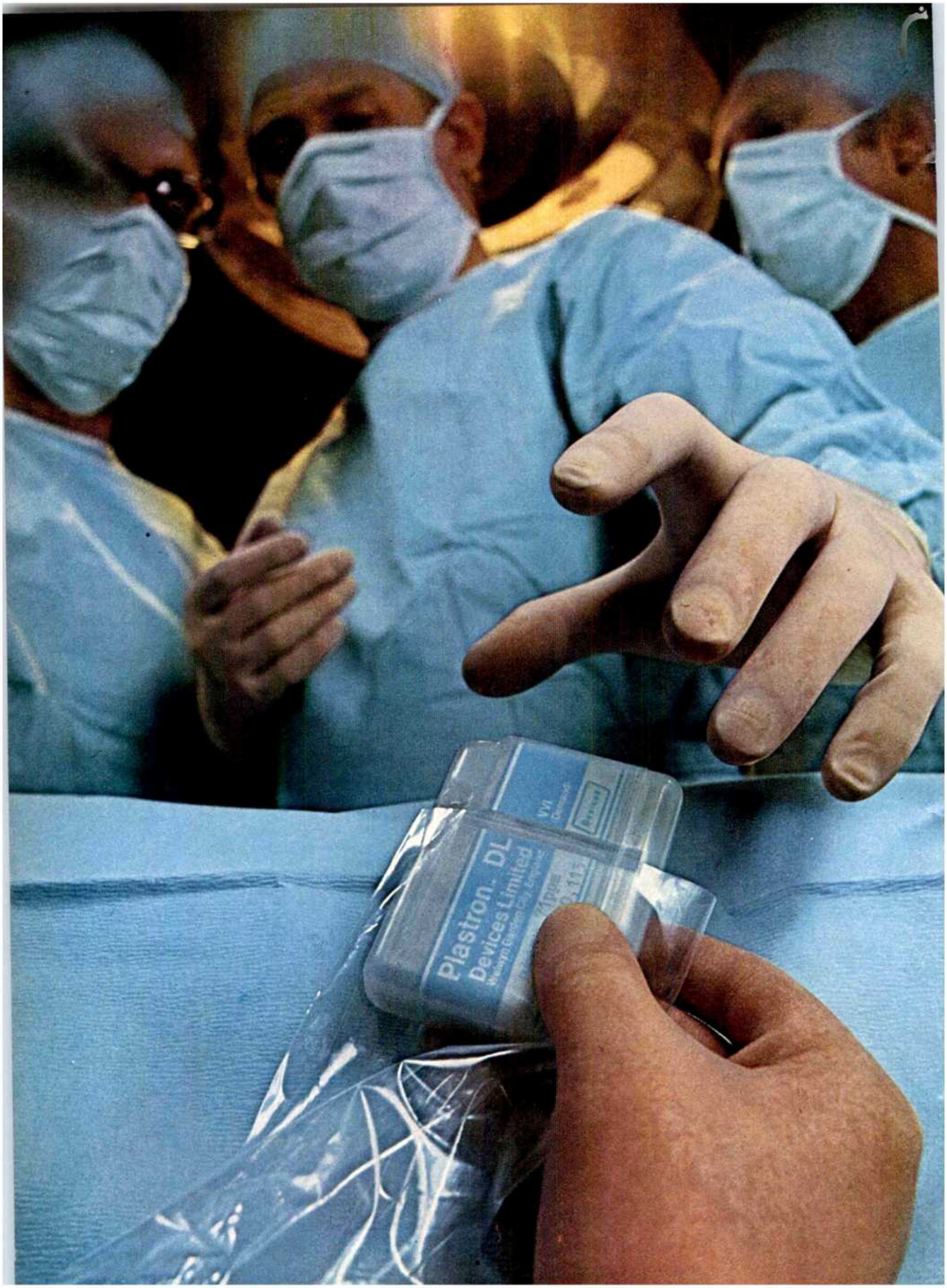
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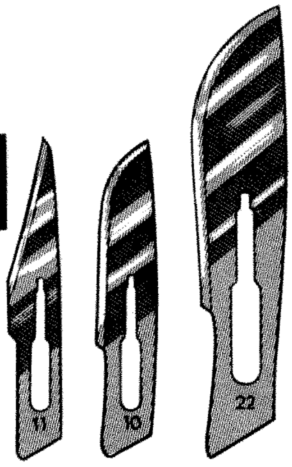

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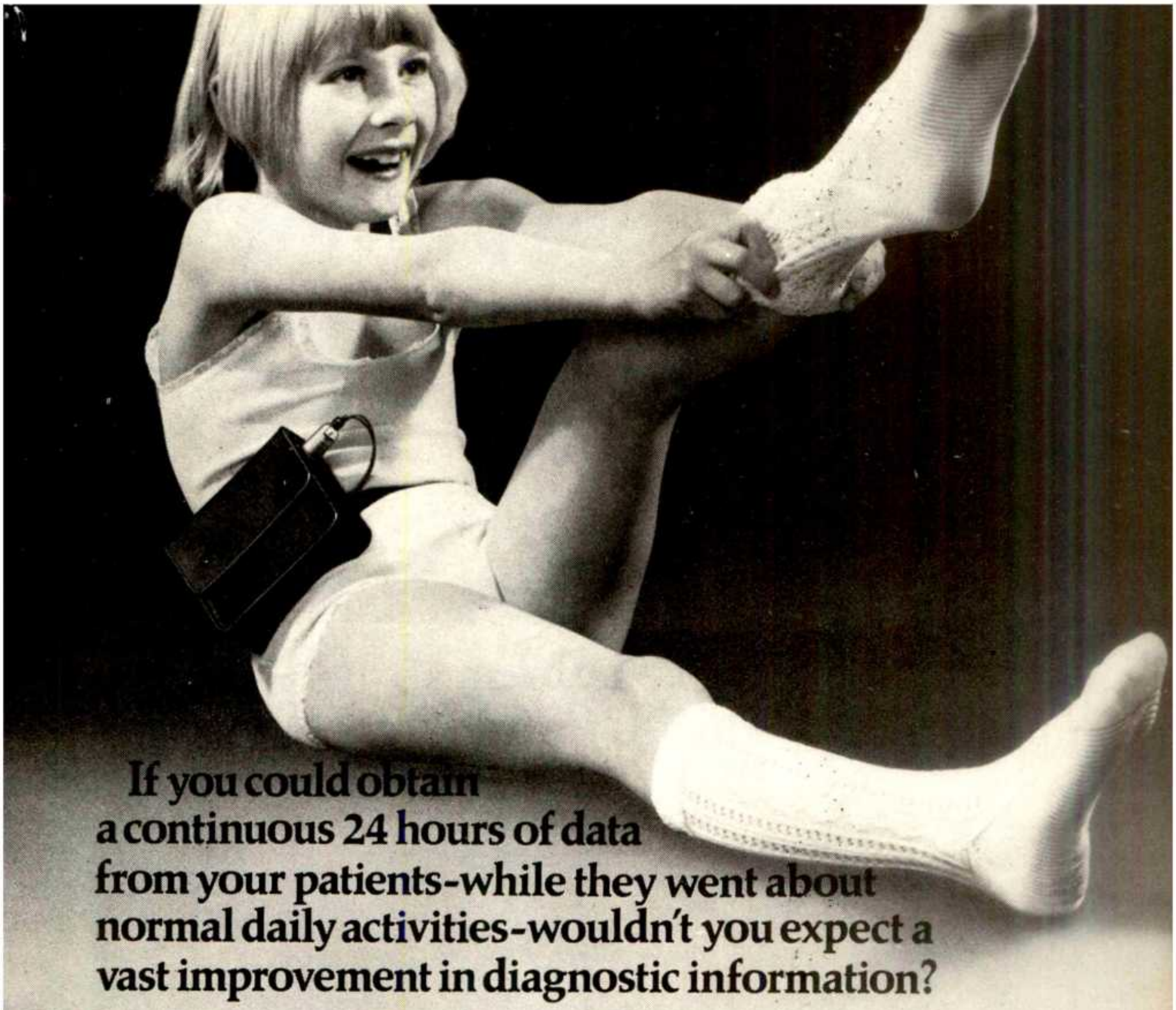

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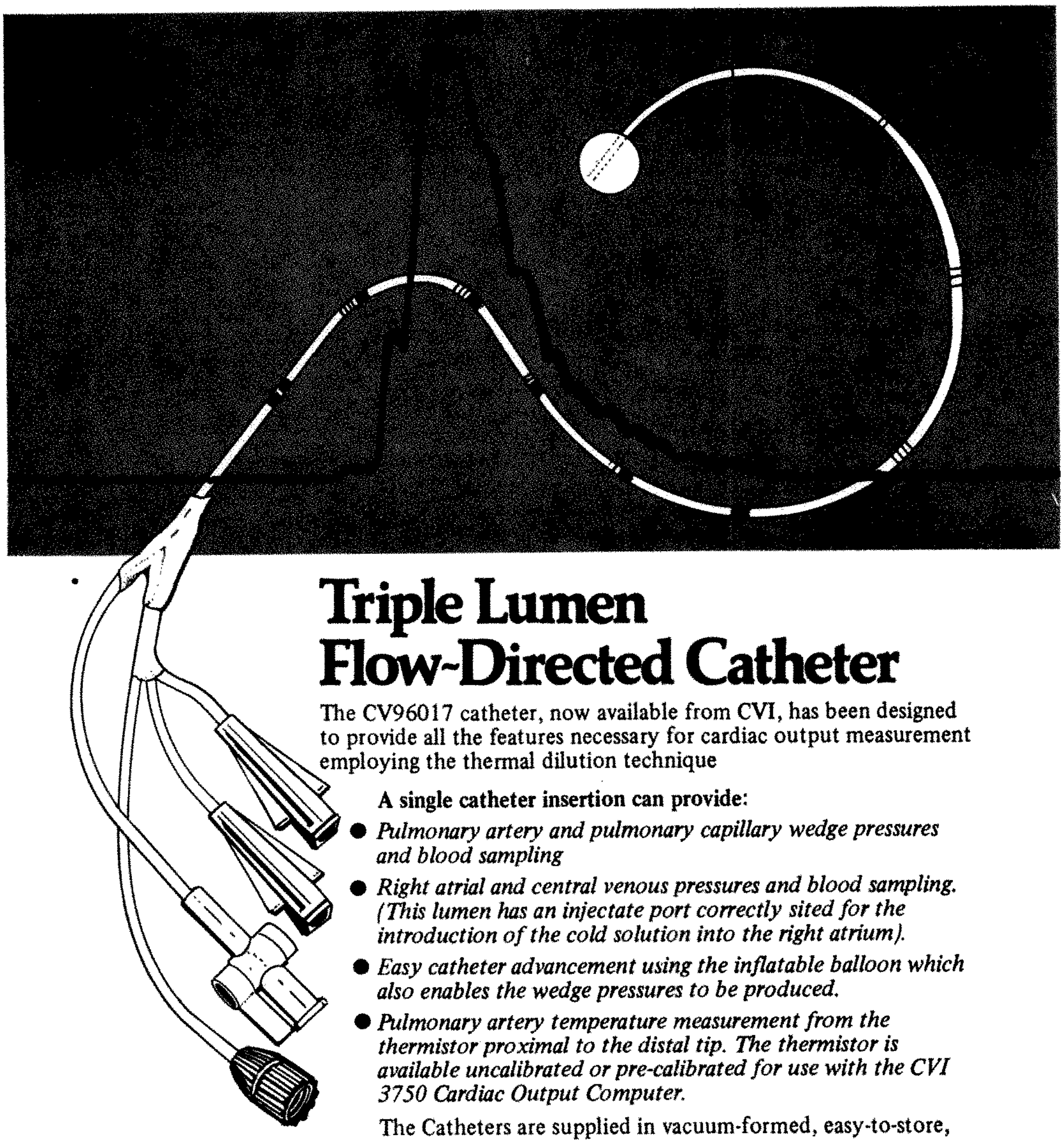

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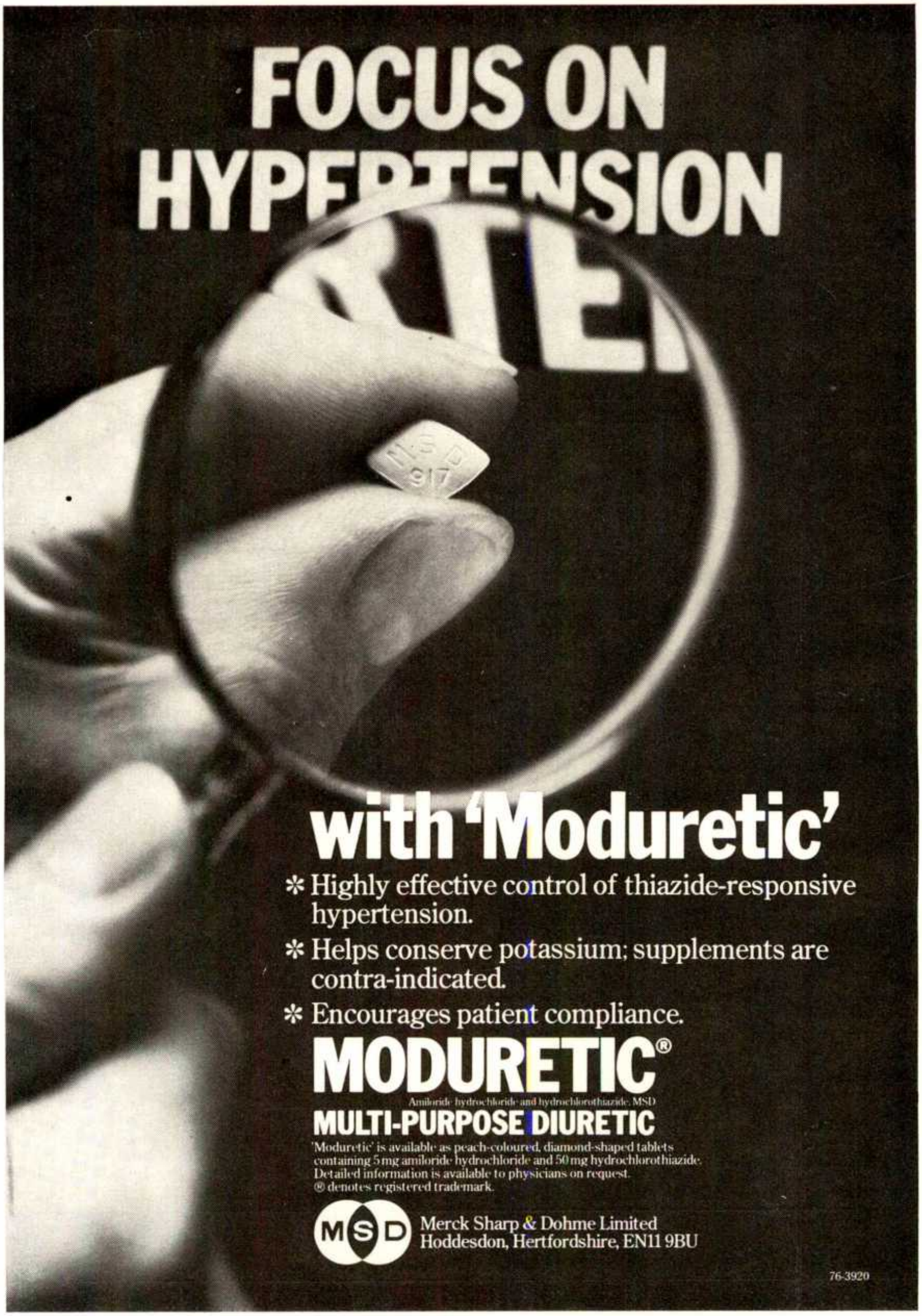

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Editorial

British Heart Journal, 1976, **38,** 433–442.

Transcutaneous aortovelography
A new window on the circulation?

Henry Light
From Bioengineering Division, MRC Clinical Research Centre, Harrow, Middx.

Clinical need

Any quantitative description of a transport system is seriously deficient if it does not include information on the volume of flow carried. Yet perforce—such are the difficulties of obtaining a reliable index of blood flow—the management of a patient severely ill with a circulatory disorder is usually based on variables, like the arterial or pulmonary wedge pressure, etc. which have only a tenuous relation to systemic blood flow. While the experience and interpretative skill of the clinician can often make some allowance for the variable and non-linear relation which these variables bear to flow, this is an unsatisfactory situation.

Much effort has, therefore, gone into the development of techniques for the measurement of a haemodynamic index which closely and reliably reflects flow. Thus a number of methods for measuring cardiac output using gas uptake or indicator dilution techniques, or electromagnetic flowmeters have been developed; these are of great value when used with care and within their limitations, which unfortunately often affect their accuracy in low-output states (Prys-Roberts, 1969; Mills, 1972; Chamberlain, 1975). However, none of these methods is well suited for routine repeated bedside use in intensive and coronary care. Most are laborious: the invasive methods, in addition, cause discomfort to the patient and are not devoid of risk. Practical problems include the difficulty often experienced in introducing catheters into a shocked patient and the delay that may occur before measurements are available.

Two other techniques perhaps have something to offer in this field. The controversy about the estimation of stroke volume by *echocardiography* has now largely died down with the realization that plausible estimates can only be obtained in the absence of dyskinesia (Gibson, 1973; Sweet *et al.,* 1975). Even when this can be excluded, the method is hardly suitable for repeated use in the wards, as reproducibility depends on a meticulous and time-consuming technique.

Thoracic impedance plethysmography (Baker *et al.,* 1971; Kubicek *et al.,* 1974) is still the subject of much controversy. Once the four electrode bands (which contribute to the stability of observations) have been applied, readings can be obtained in co-operative or passive patients during momentary interruptions of respiration. The product of the maximum rate of change of impedance and the ejection period (the latter often has to be obtained using the heart sounds) is interpreted as a measure of stroke volume. The correlations with cardiac output measurements which have been obtained in a number of studies have been variably adequate, but convincing correlations with changes in aortic blood velocity in individual patients were obtained in 6 out of 7 subjects in a pacing study (I. A. B. Brooksby and M. M. Webb-Peploe, 1976, personal communication). This technique appears to be useful for following changes in cardiac output in any one subject provided that cardiac and intrathoracic conditions do not deviate too far from normal. Rough estimates of absolute cardiac output may also be obtained under these circumstances. Little, however, has been published on practical experience with the method in intensive and coronary care. Serious problems might be expected in this area, because several extraneous factors likely to vary during treatment are capable of affecting the 'flow' signals. Some of these are the amount and distribution of extravascular fluid in the thorax (errors of –40% have been found by Baker and Denniston (1975) to arise on infusion of 100 m saline into a dog's lung), the pulsatility and timing of venous flow (Cross and Light, 1974), and the haematocrit. It is possible to allow for the error introduced by changes of haematocrit (Hill and Thompson, 1975), but only at the expense of operating convenience. Systemic and pulmonary blood pressures also might be expected to influence the signal by their effects on vascular elasticity (Becattini and della Corte, 1967), but no such effects appear to have been documented. The effects of abdominal distension are also unknown. In spite of the considerable effort which has gone into studying this technique, the precise origins of the impedance signal are still unclear, even in animals. Most of the signal probably derives from the pulsatile expansion of the major vessels, but in man the relative contributions from systemic arteries, the pulmonary circulation, and the major veins have not been established. The empirical nature of the measurement also hampers the systematic exploration of the limits of its validity (Light, 1976).

Most workers in this field have, therefore, found themselves driven back to obtaining such clues to blood flow, or changes in flow, as they can from a legion of indirect measurements and observations: blood pressure, central venous pressure, pulmonary wedge pressure, toe-to-core temperature difference, urine output and osmolality, blood gas analysis, and last but not least the patient's colour. As already noted, however, these measures are (with the partial exception of centrally-derived pulse pressures) strongly affected by other physiological variables. While this lack of specificity disqualifies them as reliable guides to body perfusion or heart action, many of them—when taken together with reliable information on systemic flow (or flow changes)—yield useful information on the other factors: the distribution of cardiac output, vascular tone, the adequacy of circulating blood volume, and ventricular filling. The limitations of some of the conventional haemodynamic measurements must, however, be borne in mind. For example, mean left atrial pressure does not necessarily represent left ventricular end-diastolic pressure (Braunwald and Frahm, 1961) and, in turn, pulmonary arterial wedge pressure sometimes is a poor indicator of mean left atrial pressure (Lozman *et al.*, 1974).

Information on central blood flow, therefore, is not only valuable in its own right, as reflecting pump function and the overall transport capability of the circulation, but it also allows more precise interpretation of the information obtained from the techniques in routine use in intensive care. Preferably, the measurement should be of phasic (instantaneous) flow because of the additional information then obtainable on the pattern of ventricular ejection and the integrity of aortic valve function. Ideally, the flow should be indicated in absolute terms. The majority of clinical requirements would, however, be satisfied if the technique yielded a variable which in any one patient was proportional to flow. This would suffice to indicate his progress or the effect of treatment on his haemodynamic status.

The new technique

This is the background against which the new ultrasonic technique of transcutaneous aortovelography (TAV), the subject of two papers in this issue (Sequeira *et al.*, 1976; Buchthal, Hanson, and Peisach, 1976), should be seen. It differs from echosonography in that what is measured is not the *position* of the reflecting interfaces (here the red blood cells), but the *speed* of their movement along the aortic arch—a variable closely related to blood flow. The principle employed, the Doppler effect, has a venerable history as a quantitative remote measurement method in fields as diverse as astronomy, aircraft control, and traffic law enforcement. In the medical sphere (Wells, 1969; Woodcock, 1975), it is in routine clinical use in a number of centres as a non-invasive means of observing fetal heart action and blood velocity waveforms in superficial vessels. Simple equipment lacking in directional resolution and linearity of response is commonly employed in the latter application (Light, 1972). Even so, much clinically useful information can be obtained when it is used within its limitations in relatively undemanding applications. The instrumentation developed for transcutaneous aortovelography differs in that it retains the linearity and the potential for once-for-all-time calibration which are inherent features of the Doppler measurement principle. It also seems to have largely overcome problems associated with the intrathoracic position of the aorta, and its proximity to other vessels (Light and Cross, 1972; Light, 1974; Cross and Light, 1974).

The technique should allow the operator, who might be a nurse or technician, to measure blood velocity in the aortic arch in the majority of subjects. Multi-observer reproducibility trials in which Fraser *et al.* (1976) found the coefficients of variance to be less than 8 per cent suggest that inexperienced operators can obtain reproducible recordings of what—from theoretical considerations and circumstantial evidence—is likely to be the absolute value of 'mainstream' blood flow velocity in the proximal descending aorta. *This variable should be a useful near-quantitative index of relative systemic flow under most circumstances.*

Evidence for this is provided in one of the papers now published (Sequeira *et al.*, 1976).

Here it need be noted only that the observed blood velocity is linked to flow in the transverse aorta by two factors (and to cardiac output by three factors) which can, as a first approximation, be treated as constant in any one patient over a fair range of conditions. These are, the cross-sectional area of his aorta, and secondly, the transverse velocity profile in it. The third factor, the fraction of the cardiac output which flows into the transverse aorta, enters into the relation only when changes in cardiac output are to be deduced. When these factors remain exactly constant during serial measurements in any one subject, systemic blood flow will be exactly proportional to the indicated velocity, so that the latter is an exact index of what can be referred to as *relative flow*, i.e. the ratio of two serial blood flow values. The rationale for treating these factors as substantially constant under many practical conditions is not that they are truly invariable—for assuredly at least aortic dimensions and the distribution of cardiac output are not—but that under most clinical conditions their variations are sufficiently small compared with simultaneous changes in blood flow that velocity changes can represent changes in volume flow in a near-quantitative manner.

An estimate of the likely error introduced by the assumption of constant aortic cross-section can be derived from Goldberg's large series of echosonic *in vivo* measurements of diameter changes with pulse pressure in the proximal part of the human aortic arch (Goldberg, 1971). Typical diameter changes of 7 per cent were observed. These suggest that when a fall in blood flow of, say, from 5 to 2·5 litres per minute is accompanied by a fall in systolic blood pressure by 45 mmHg (6·0 kPa), the observed blood velocity will typically fall to 58 per cent of its previous value compared with the 50 per cent fall in flow. Greater divergence between flow and velocity ratios will occur in patients with highly elastic vessels and for greater falls in blood pressure, but, otherwise flow changes will be more accurately reflected by velocity changes.

The transverse velocity profile within any individual aorta would be expected to remain constant as long as the architecture of the proximal aorta is not altered. Supportive evidence is discussed in Sequeira *et al.* (1976).

While the accuracy with which flow changes in the transverse aorta can be deduced from velocity changes will thus depend on the circumstances, the errors involved are—with one exception (pathological deformation of the proximal aorta between measurements)—likely to be small (perhaps trivial) compared with those which may be involved in deducing flow changes from the indirect measurements (BP, central venous pressure, PA wedge pressure, AV oxygen difference) which are in common use.

Experimentally, as reported in this issue, good proportionality was found between measurements by transcutaneous aortovelography and measurements of blood velocity and flow by invasive techniques, under clinical conditions. Comparisons with acetylene uptake studies, made with Dr. Brotherhood, suggest that proportionality also extends to changes with exercise (Light, 1974). Other workers have reported similar findings with closely related techniques (Mackay and Hechtman, 1975; Huntsman *et al.*, 1975). They confirm also that recordings can be simply and quickly obtained in the majority of patients and that the technique is compatible with the routines of clinical care. Preservation in the recording of the full spectral information helps to indicate when a transducer placed on the suprasternal notch of the supine patient is properly aimed towards the aortic arch. The power levels of ultrasound involved (less than 50 mW/cm^2) are most unlikely to present any safety hazard (Curzen, 1972; Ulrich, 1974; Wells, 1974).

The recordings of instantaneous (phasic) blood velocity, which are obtained by transcutaneous aortovelography, yield not only an approximate index of time-averaged flow, but also allow the manner of ejection of blood from the left ventricle to be observed. As discussed below, additional information which can be obtained from the velocity wave form about variables such as flow period, early systolic acceleration, peak velocity, and the duration of any turbulence present, is likely to be of clinical value.

What are the *disadvantages* of the technique? While reproducibility has been shown to be good and there is circumstantial evidence that the technique indicates a particular blood flow velocity with reasonable accuracy, we suggest that only *relative volume flow* should be deduced from this at present. Calculations of *absolute volume flow*, using independently derived information on aortic diameter, involve assumptions that (a) the transverse velocity profile is perfectly flat, and (b) the aortic cross-section is circular. Our findings suggest that such calculations of absolute flow sometimes yield values which are too inaccurate for anything much more demanding than the differentiation of hyperdynamic from hypodynamic conditions. When knowledge of absolute cardiac output is essential, a single 'calibration' measurement on the particular patient by another technique is required.

The *reliability* of this remote-sensing technique

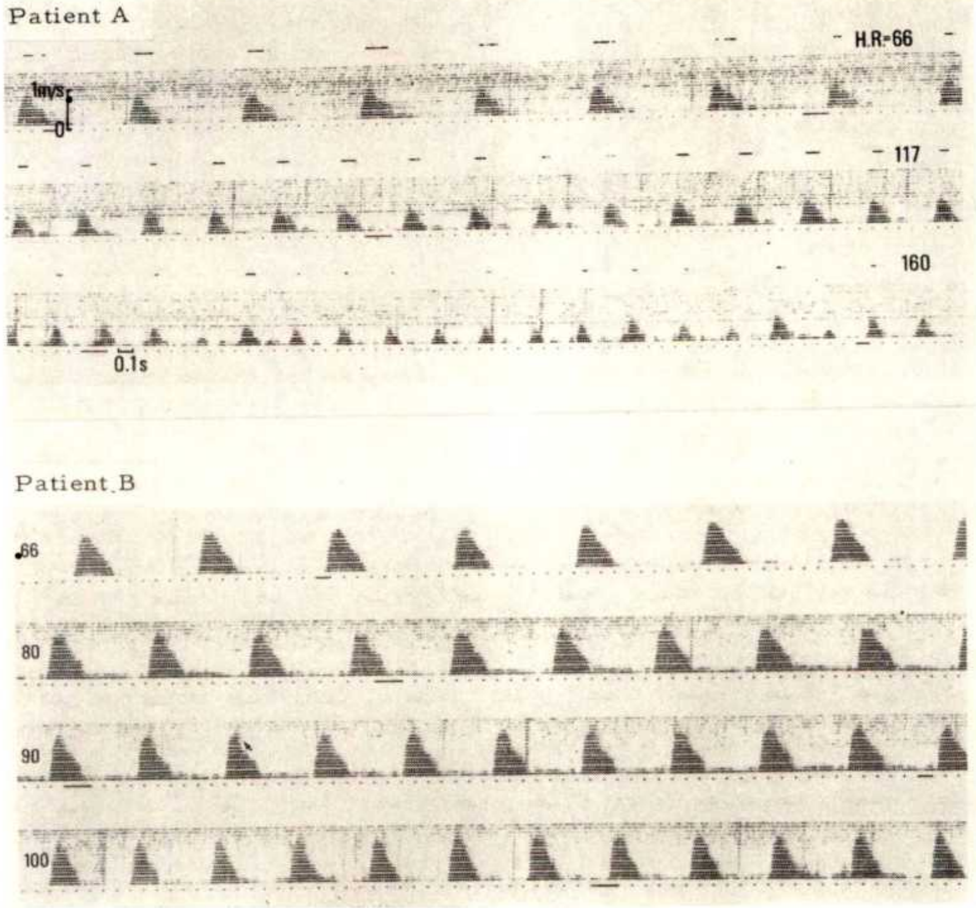


FIG. 1 *Non-invasive aortic blood velocity recordings by transcutaneous aortovelography, taken at various pacing rates during diagnostic catheterization of two patients with suspected ischaemic heart disease. Phasic blood velocity during systole is indicated by the outline of the dark complexes. The velocity (vertical) and time (horizontal) scales are identical in all recordings.*

Although all aspects of the wave form (including early systolic acceleration and the duration of systolic flow) are affected by pacing rate in the two patients, the peak velocity and the area of the complex (an index of stroke volume) show the most obvious differences. The transient response to changes in heart rate (not illustrated) also differed in the two patients. It is hoped that similar studies of the response to non-invasive interventions may contribute to the practical assessment of left heart function. (From studies conducted with Dr. R. F. Sequeira.)

has been extensively investigated (Light, 1974; Light *et al.*, 1976). The apparently complex grey-scale spectral recording, which is provided (Fig. 1), allows the wanted blood velocity information to be distinguished from artefacts. Results appear to be trustworthy whenever the appearance of the aortic velocity outline satisfies some simple criteria (Light, 1976). Dubious readings, which are occasionally obtained, can thus be recognized and discarded. The need for inspection of the record, however, implies that wholly automatic data extraction is not feasible at present. The bedside quantification of edited recordings is nevertheless conveniently achieved by the use of mechanical aids or a free-stylus planimeter (Light, Lowe, and Rosenthal, 1974b) developed for this purpose.

Adequate signals cannot be obtained from the body surface in patients in whom ultrasonic access is obstructed by tracheostomies, or surgical emphysema, and also from a small proportion of other subjects. (An alternative approach, by an oesophageal probe, may then be appropriate: Olson and Cooke, 1974; Duck, Hodson, and Tomlin, 1974.) In a further proportion of subjects, from whom only barely adequate signals are obtained, patience and experience are required to produce usable recordings.

Finally, mention should be made of two major practical disadvantages: (1) Because relatively complex signal processing is involved, the instrument will be more expensive than, say, an electrocardiograph; one instrument, however, can cover a ward or department. (2) The technique and the variables observed are relatively novel and the relevant published material is therefore sparse: aortic blood velocity observations have hitherto been largely restricted to sedated cardiac patients with the type and severity of disease that warrants catheterization. However, as the technique is non-invasive and relatively simple, a clinician can rapidly familiarize himself with it and the interpretation of the data obtained.

Potential value of transcutaneous aortovelography

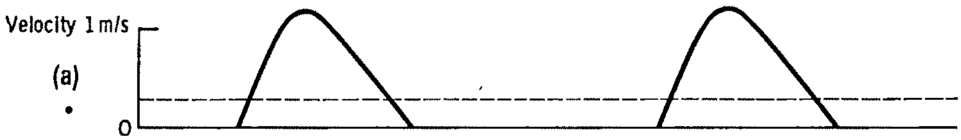
It is possible to foresee ways in which this new technique will add to our understanding of the behaviour of the circulation in health and disease. The observation that some hypotensive agents produce predominantly a reduction of peripheral resistance and others a reduction of cardiac output was not unexpected (Birkenhäger *et al.*, 1975; Light *et al.*, 1976). On the other hand new questions will be asked, and new perspectives gained.

For example, clinically useful information may be obtained by analysis of various aspects of the velocity wave form in states of depressed left ventricular function (Hanson and Buchthal, 1976). Pathological changes are not confined to the slope of the leading edge of the systolic complex, representing early systolic acceleration (dV/dt), which is an index of left ventricular 'contractility'. Major changes also take place in other aspects of the wave form (e.g. peak velocity, deceleration, and ratio of systolic to diastolic period). It became apparent that much of what has been established by work on anaesthetized animals is not directly applicable to unsedated or lightly sedated man, for reasons that have been summarized by Vatner and Braunwald (1975). A pilot examination of what can be deduced from the waveform was conducted with an eye on the pressing practical problem of assessing left ventricular function in patients. This has led to a closer definition of the possibilities and to the appreciation that another clinically important variable might be measured—an index of the neurocirculatory status of the critically ill patient.

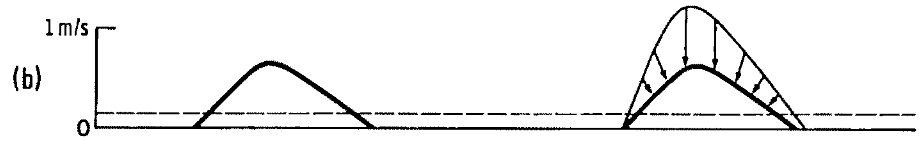
In general it is necessary to distinguish between various circulatory operating 'regimens' which impose differing constraints on the regulatory mechanisms—whether the patient does or does not possess some cardiac reserve, and whether left heart function or venous return governs cardiac output. (The transient response to a sudden stimulus—observable only by a beat-by-beat method—should allow differentiation between the latter alternatives: a greater short-term enhancement of stroke volume may, for example, be produced when dilated pulmonary veins hold a reservoir of blood.) The heart normally possesses considerable functional reserve, so that the distinction between actual functional state and the potential functional capability is important—hence the widespread use of exercise and other stress tests. Whenever this functional reserve is positive, extrapolation from an observation of functional state to an estimate of capability would require precise information about the factors, including the intensity of autonomic nervous stimulation and the biochemical *milieu*, which define the inotropic state at the time of observation. Neither this sort of information, nor the knowledge of how to carry out the extrapolation, is at present available. Some such information may, however, become available from inspection of the wave form, if the suggested interpretation of the wave form changes illustrated in Fig. 2 applies also when some cardiac reserve is present.

We would therefore suggest that if valid deductions of left ventricular capability are to be based on haemodynamic measurements, observations of the response to such interventions as exercise, change of posture, non-invasive sequestration and controlled release of part of the circulating blood volume, etc. will be required, rather than single measurements (Light, Cross, and Hansen, 1974a). This proposition has not yet been seriously examined, but observations of the wide individual variations in the response of the aortic velocity waveform to changes in heart rate with pacing (Fig. 1) suggest that some progress may be possible along these lines. This reasoning also leads to another hypothesis, that the interpretation of the observations might be simpler in patients who were known to have inadequate cardiac output at rest, because the problems associated with the existence of a positive functional reserve would then presumably be absent.

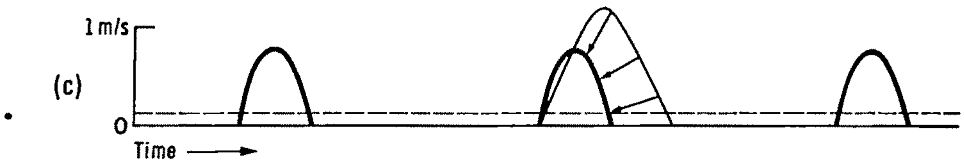
As it is generally accepted that one result of impaired left ventricular function, whether this is the result of diffuse myocardial involvement, a focal lesion, uncoordinated excitation, or inadequate



Normal systolic waveform in adults (for comparison).



Primary effect of impaired left ventricular function.
Seen comparatively rarely in critically ill patients - probably associated with depressed response of (or to) the sympathetic system.



Waveform usually seen in patients stressed by inadequate circulatory function.
(Reflects combined effect of impairment and sympathetic 'compensation').

FIG. 2 *A diagrammatic representation of the time-course of aortic blood velocity, as seen in patients with gross impairment of circulatory function, with suggested interpretation. The index of central blood flow obtained from transcutaneous aortovelograph recordings is the time-average of the indicated phasic blood velocity (dashed line). Different ways in which this may be depressed are illustrated by the blood velocity waveforms (b) and (c). The deviation from what might be a typical normal waveform at the corresponding heart rate is also indicated.*

If it is verified that waveform (b), expressing the primary depression of left heart function, is indeed transformed by sympathetic stimulation into waveform (c), as commonly seen after severe myocardial infarction or in hypovolaemic shock, it may prove possible to derive indices from aspects of the waveform which separately indicate the degree of primary myocardial depression and of reactive sympathetic stimulation. Note that the early systolic acceleration (dV/dt) of aortic blood velocity in waveform (c) is paradoxically high only when compared with normal subjects at rest. A more appropriate comparison might be with normals in a state of increased sympathetic tone.

filling pressure, is a reduction in contractility, we expected to find low values for the early systolic acceleration (dV/dt) under these circumstances. A wide range of observations on patients with severely depressed haemodynamic status in intensive and coronary care, however, showed that the majority had *raised* values of dV/dt compared with normals at rest. Associated findings were that the duration of systolic flow was much shorter than normal for the particular heart rate, peak velocity was reduced, and the area under the velocity wave form, an index of stroke volume, was grossly depressed. Fig. 2c shows the wave form commonly seen in these patients.

A possible explanation for these findings is that the observed increase in dV/dt and shortening of the ejection period is a response to the sympathetic stimulation which is known often to accompany inadequate output. It is suggested that the primary circulatory depression results in the waveform of Fig. 2b and that increased sympathetic stimulation not only increases the heart rate, but converts what would otherwise be a pathologically slow but sustained myocardial contraction into an apparently vigorous but disproportionately brief movement. Some support for this view comes from instances when the expected primary depression of dV/dt (Fig. 2b) has in fact been seen: these include subjects under deep halothane anaesthesia and some with diabetic neuropathy. Depression of dV/dt has also been seen in catheterization studies on patients with ischaemic heart disease (Bennett *et al.*, 1974; Jewitt *et al.*, 1974). It will be interesting to establish whether the broad difference between these observations on one hand, and those in intensive and coronary care units on the other, is the result of differences in the severity of the haemodynamic disturbance, acuteness of its onset, the sedation used, or other factors (Shillingford and Thomas, 1967).

The high observed dV/dt values may also in part be caused by an abnormally low afterload, i.e. low peripheral resistance, in many hypotensive intensive care patients. Reduced afterload would not account, however, for the shortening of systole, and it probably contributes only little to the 'paradoxical' increase in dV/dt (van den Bos *et al.*, 1973). The relatively intense reflected pressure wave from the periphery, which is found in vasoconstricted patients (Mills *et al.*, 1970; McDonald, 1974), and is an indirect result of increased sympathetic activity, may contribute to the shortening of systole but is not thought to be a major factor: in many hypotensive patients systole is indeed over before this reflected wave arrives at the measurement site.

If the interpretation of the waveform put forward in Fig. 2 indeed allows differentiation between the primary deficit and the reflex reaction, this should contribute to an assessment of left ventricular state as well as providing an indicator of pathological 'stress' (Bushman, 1973). An increase in early systolic acceleration without concomitant increase in an abnormally low ratio of systolic to diastolic period might thus be an indicator of increased sympathetic activity. Some observations suggest that this type of change is an unfavourable sign (Hanson and Buchthal, 1976). Any estimate of depression of myocardial function thus obtained is likely, however, to be very approximate. The observed similarity of velocity wave forms in severe hypovolaemia and in severe myocardial ischaemia suggests that further differentiation between extrinsic and intrinsic causes of myocardial depression is unlikely to be feasible on the basis of static observations alone. Observation of the effect of interventions, such as trials of specific therapeutic measures, will again be required. For example, while adequate volume replenishment will restore blood velocity to normal if the *sole* cause of depressed function is hypovolaemia, the response to blood volume adjustment will be less in subjects with cardiac lesions. Presumably these changes are the result of adjustment of the atrial pressures to allow the heart to operate at the maximum of whichever ventricular function curve is limiting the cardiac output.

Some other observations of pathophysiological interest concern the *distribution of cardiac output and abnormal venous flow patterns*. When normal cardiac output is restored after a period of relative ischaemia, relaxation of the peripheral vasoconstriction is not necessarily immediate. Normal or hyperdynamic conditions may be seen in the descending aorta under these circumstances for perhaps two hours before limb perfusion returns to normal. A possible explanation is that the phenomenon of reactive hyperaemia, familiar in the peripheral circulation, may also occur in the central circulation and for a time predominate. Signals from venous flow, probably from the innominate vein, are often also incidentally observed. They can be resolved from aortic signals as they normally appear in a different shade of grey and have a different wave form, which is elongated, with relatively low Doppler shifts and strong respiratory variation. In occasional patients with serious circulatory impairment, however, a very different venous flow pattern is seen (Cross and Light, 1974): this resembles arterial flow in having near-triangular wave form, very high peak velocities (equalling or exceeding those in aortic flow), but is diastolic in timing. The circumstances associated with this phenomenon, which probably accounts for the diastolic peak sometimes seen on thoracic impedance plethysmograph recordings (Kubicek *et al.*, 1974), still have to be elucidated.

Applications to patient assessment and management

While the above are examples of unfamiliar phenomena seen through this new 'window on the circulation', most observations are readily interpreted. This applies particularly to the (usually simultaneous) increases in peak velocity, flow duration, and time-averaged (mean) velocity, which reflect an improvement in body perfusion. Even in such instances, however, more sophisticated analysis of the data may well give more detailed information of clinical value about the state of cardiac function and the circulatory system. Taken together with the measurements conventionally used in the care of the critically ill patient, non-invasively acquired aortic blood velocity data should give a fuller picture of the changing haemodynamic status than has hitherto been readily available. In particular, the patient's immediate response to various therapeutic interventions should be a guide to optimum management in many situations during intensive care. Thus, if blood flow is seen to respond positively to a trial infusion of fluid (Bradley, Jenkins, and Branthwaite, 1970;

Loeb *et al.*, 1973) and the central venous pressure does not rise excessively, volume expansion may be continued until the optimum loading, which will be signalled by a falling-off in improvement, is approached. Further improvement of cardiac output may then be achieved by the monitored use of inotropic and/or afterload-reducing agents (Wyse, Gibson, and Branthwaite, 1974; Hood, 1975). Such closely supervised therapy might be expected to yield better results than these measures used singly or blind. In other patients, the technique may be valuable to check on the effects of ventilator or pacemaker adjustments.

The cardiologist, in addition, should find the wave form abnormalities seen in aortic valve disease and hypertrophic obstructive cardiomyopathy of interest (Light, 1974). Visualization of blood velocity in the pulmonary artery, which can (with somewhat greater difficulty) be carried out in children by the same instrument (Cross, Light, and Sequeira, 1974; Cross and Light, 1974), may assist the paediatrician in the non-invasive diagnosis of congenital defects.

Possible future developments

The information provided by transcutaneous aortovelography complements that given by echocardiography; it supplements the pictures of intracardiac structure and local function (Gibson and Brown, 1976; Weissler, 1974) obtained by the latter by providing a measure of *overall* left heart function. For diagnostic purposes, these two non-invasive ultrasound techniques may be joined by a third—a range-gated narrow-beam Doppler technique for examining the timing and nature (laminar or disturbed) of local flow through the heart valves (Baker and Johnson, 1975; Angelsen, Aaslid, and Brubakk, 1975). Such instruments for sensing highly localized blood motion may indeed be incorporated in 'duplex' echocardiography units. However, because of the increased difficulty in obtaining reproducible data on aortic flow velocities with highly selective instruments, the latter are unlikely to compete with transcutaneous aortovelography for serial observations of relative systemic flow. (Complexity of operation and difficulties of access also appear to preclude the transcutaneous application to the deep thoracic vessels of the multi-gate pulsed Doppler techniques (Histand, Miller, and McLeod, 1973; Doroit *et al.*, 1976) now being developed for the measurement of absolute flow.)

Techniques derived from transcutaneous aortovelography, but with different (simplified) signal processing and/or display methods, are being investigated in several centres (Huntsman *et al.*, 1975). Thus Boughner has shown that in expert hands limited objectives (the quantification of aortic and mitral regurgitation) can be achieved with simpler signal processing (Boughner and Nicol, 1974; Boughner, 1975). Such variants, however, must be distinguished from the parent technique, as there is much evidence to suggest that 'simplification' is attended by sacrifices in one or more important features of transcutaneous aortovelography: reliability of serial flow estimations, suitability for use by non-specialist personnel, and speed of data acquisition. It is probable that greater operational convenience than has already been attained by transcutaneous aortovelography can be achieved, but more complex signal processing will be required if the present visual data extraction from a spectral display is to be replaced without loss of reliability by the use of, for example, an analogue output which directly indicates aortic blood velocity.

Conclusion

In summary, transcutaneous aortovelography is a non-invasive ultrasound technique, based on a well-understood quantitative principle, for recording the phasic mainstream blood velocity in the human transverse aorta. Reproducibility studies suggest that velocity changes exceeding 10 per cent can be detected with greater than 90 per cent confidence. Serial velocity measurements appear to give a useful near-quantitative measure of changes in blood flow in the central circulation and also to indicate some of the characteristics of left ventricular ejection on a beat-by-beat basis.

Sufficient laboratory and clinical experience has now been gathered for an early assessment of its clinical potential: clues to the state of the patient are given by several aspects of the instantaneous velocity wave form. Serious hyperdynamic and hypodynamic conditions appear to be indicated by abnormalities of scale, and most lesions of the left ventricular outflow tract are marked by characteristic irregularities. Transcutaneous aortovelography is likely to prove a simple way of quantifying regurgitation (which is indicated on a bidirectional display) and for reviewing prosthetic valve function during follow-up. The range of abnormal wave forms seen in severe circulatory depression is believed to reflect the degree of sympathetic response to the primary functional disturbance, and illustrates the importance of examining the whole of the systolic velocity wave form. Observation of the effect of diagnostic or therapeutic interventions is likely to give further useful information in assessment of patients. Greater flexibility in patient management and a closer approach to optimal therapy may result from the immediate and continuing feedback of data relating to the patient's haemodynamic response, which is conveniently made available by transcutaneous aortovelography.

It is a rash man who attempts to set into perspective a technique which he has helped to develop. The danger of prejudice is great, and I cannot hope to have escaped it entirely. It is an even rasher man, who as a non-clinician, also engages in some of the more controversial issues of cardiology. I hope, however, that these observations will contribute to the debate. I am most grateful to the many clinicians upon whose experience I have drawn, notably Drs. G. C. Hanson and D. C. White, who have shared and discussed their findings with me, to Professor E. N. Terry, Dr. H. L. Green, Dr. J. G. Jones, and Mr. H. S. Wolff for critical comments on this manuscript, and to Mr. G. Cross and other colleagues for their technical help. The responsibility for misinterpretations and for the more speculative elements in the above discussion is however mine alone.

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Transcutaneous aortovelography
A quantitative evaluation

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The haemotachograph is a non-invasive ultrasonic Doppler-shift instrument designed to measure the velocity of blood in the arch of the aorta by a technique referred to as transcutaneous aortovelography. Its accuracy has been assessed at cardiac catheterization in 20 patients. When transcutaneous aortovelographic values were compared with stroke volume determined by standard invasive techniques, a good proportional agreement was found. The accuracy of absolute flow values, as calculated from transcutaneous aortovelography and dimensional data, was, however, poor. Peak velocity determined from transcutaneous aortovelographic tracings agreed well with values obtained with a catheter tip electromagnetic velocity probe. Transcutaneous aortovelography is a useful non-invasive technique which can be used to determine phasic blood flow velocity in the aortic arch and to follow changes in cardiac output over a period of time.

Most available methods for measuring cardiac output and the haemodynamic indices which are thought to provide a measurement of cardiac functional status require that catheters or flow probes be inserted into arteries and accurate measurements made under static and strictly controlled conditions (Cliffe, 1973; Mills, 1972). Established non-invasive methods for measuring cardiac output (Pugh 1972; Bosman *et al.,* 1964; Karatzas *et al.,* 1967) depend on a constant ventilation—perfusion ratio in the lungs and thus have obvious limitations when used under clinical conditions. Ultrasonic methods for estimating ventricular volumes have proved useful in valvular disease (Feigenbaum *et al.,* 1969; Feigenbaum, 1974) but difficulties arise when ventricular dysnergy is present (Heikkilä *et al.,* 1972; Gibson and Brown, 1974). The development of a Doppler-shift ultrasound instrument by Light and his co-workers (Light and Cross, 1972; Light, 1974; Light *et al.,* 1974; Cross and Light, 1974) provides a non-invasive measurement of blood velocity in the arch of the aorta and promises to be a useful advance in non-invasive technology. We have assessed the performance of this instrument in measuring stroke output and peak velocity, by comparing it with standard invasive techniques.

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Materials and methods

The instrument (Fig. 1) consists of a direction-resolving Doppler unit which allows the separate analysis of coexisting signals from advancing and receding flow, a Doppler probe containing both transmitting and receiving transducers, and an on-line spectral analyser. It is compact and mobile and can conveniently be moved to the bedside. Unlike much of the conventional Doppler instrumentation, it retains the linearity and lack of need for calibration which are intrinsic to the Doppler phenomenon. Transcutaneous aortovelography is the name that has been given to this technique for sensing

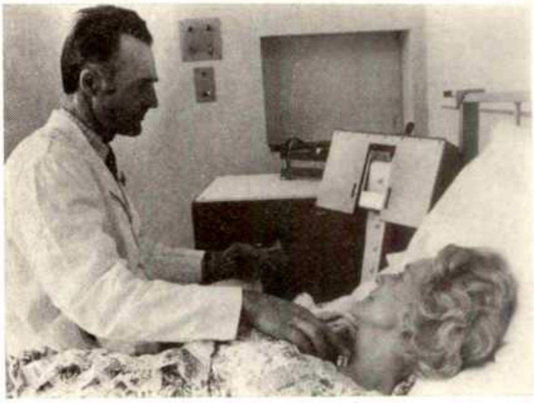

FIG. 1 *The non-invasive haemotachograph in use.*

blood velocity and the instrument has been named the non-invasive haemotachograph.

Basic theory of transcutaneous aortovelography

If a vibration of a known frequency, F, is backscattered by a target moving with a velocity V at an angle θ to the direction of incidence of the vibration, the backscattered energy will have a frequency $F \pm \Delta F$, where ΔF, the Doppler shift, is given by $\Delta F = \frac{2F}{C} V \cdot \cos \theta$. As c, the propagation velocity of the vibration in tissue, is known to within 1 per cent and F has a value which is precisely known for a particular instrument, $V \cos \theta$ can be accurately calculated from the Doppler shift ΔF, without need for calibration.

To obtain the velocity V of the moving target, the angle θ must be known, except for the special case when it is close to zero. In that case, provided θ is less than 25°, $\cos \theta$ can be taken to equal 0·95 with a maximum error of ±5 per cent, thus allowing the actual velocity V to be calculated within that margin of error. The sign of the Doppler shift indicates whether flow is towards (+) or away (−) from the probe containing the transducers.

In order that signals from tissue vibrations do not interfere with the analysis of the wanted signals from blood flow, low Doppler shifts (corresponding to in-line velocities of less than 10 cm/s) are suppressed. Thus very low velocities, as occur during diastole, cannot be seen, but the measurement of higher velocities is not affected.

Technique for using haemotachograph

The arch of the aorta is a suitable vessel for transcutaneous aortovelography because its anatomical position allows the ultrasonic beam to be closely aligned with the direction of flow (Fig. 2) and the angle θ is likely to be less than 25° (Light, 1974). Furthermore, this part of the aorta carries most of the cardiac output and so the results are not unduly affected by regulatory mechanisms confined to any one kind of vascular bed, and it is close enough to the heart to reflect changes in left ventricular function.

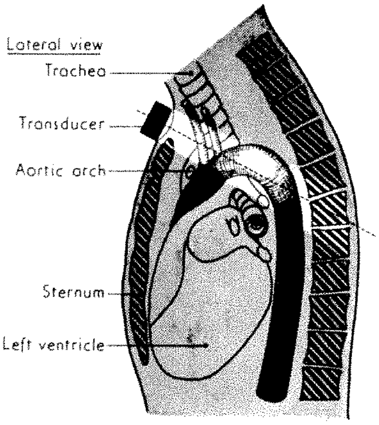

FIG. 2 *Probable path of ultrasonic beam. The sagittal section illustrates the in-line incidence of the ultrasonic beam to the arch of the aorta. The highest Doppler shifts come from the part of the vessel shown in white.*

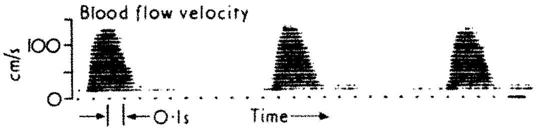

FIG. 3 *On-line transcutaneous aortic velocity recordings. The outline of the darkened areas is the velocity waveform, and the area under the systolic velocity curve should be proportional to stroke volume.*

To obtain the signal, the Doppler probe is applied to the suprasternal notch and pointed towards the aortic arch. Using the sounds produced by the processed Doppler-shift frequencies and the recording as a guide, the probe is manoeuvred so that systolic flow complexes of clear outline are obtained (Fig. 3). As viewed from the transducer, systolic blood flow in the arch of the aorta is receding and thus gives negative Doppler shifts. To ensure selective analysis of aortic flow, only negative Doppler shifts are analysed and displayed. The *highest* Doppler shift at any one time, which appears as the *outline* of the waveform, measures the highest instantaneous blood velocity within the vessel. Lesser frequency shifts are also returned from regions near the vessel wall and those parts of the vessel carrying flow at a substantial angle to the beam, but since attention is paid only to the outline of the waveform these are automatically discounted. Because of its inclination to the beam, pulmonary artery flow also will normally return only lesser shifts of frequency, and, therefore, not interfere with the measurement.

Relation between measured variable and flow

The variable indicated by transcutaneous aortovelography is thus the highest flow velocity existing in the insonated part of the transverse aorta at any one time. This is a good index of the flow velocity averaged over the whole cross-sectional area of the vessel, providing the transverse flow profile in the particular subject remains substantially constant (a) throughout systole and (b) between serial measurements. Several studies (e.g. Schultz *et al.*, 1969) have shown that flow profiles do not change greatly throughout systole. Moreover, on fluid dynamic grounds, the profile should normally remain constant in any one subject over lengthy periods of time. (Changes to the flow profile are, however, to be expected if the aortic tract is deformed, e.g. by a tumour progressively compressing the aorta around or proximal to the measurement region. Under such circumstances, blood velocity measurements by transcutaneous aortovelography will be directly comparable as an index of flow only over relatively short periods.)

When, as is normally the case, the transverse flow profile is relatively flat, the velocity measured by transcutaneous aortovelography will approximate to the average velocity throughout the vessel. However, serial transcutaneous aortovelographic measurements in any one subject are meaningful indices of blood velocity *whatever* the flow profile happens to be, provided only that the profile remains constant in that subject.

For velocity to be an accurate index of flow, it is further necessary that the cross-sectional area of the vessel remains constant between measurements. This is unlikely to be exactly true for an elastic vessel like the aorta, but non-invasive observations suggest that under most circumstances the magnitude of the changes is not such as to introduce major errors.

For a fuller treatment of the theoretical bases, see Light (1974) and Cross and Light (1974).

One might, therefore, expect that, with relatively rare and largely predictable exceptions, transcutaneous aortovelography will give readings which are approximately proportional to those produced by other velocity of flow indicating methods. Identity of readings with other velocity-sensing techniques would, however, be expected only if these measured the same variable as transcutaneous aortovelography, namely the highest flow velocity in the insonated region of the aorta.

The studies reported here were intended to test these expectations.

Analysis of transcutaneous aortovelographic signals

A drawing indicating how the various measurements are extracted from the waveform is shown in Fig. 4. The outline of the area is the velocity waveform and the area under the systolic velocity curve should be proportional to stroke volume (see Appendix). In order to calculate this area and hence the mean velocity, the waveform was treated as triangular (Cross and Light, 1974). Mean velocity, $\bar{v}$, is obtained by dividing the area by the duration of the cardiac cycle. Peak velocity is easily measured and the slope of the tangent to the early part of the waveform represents acceleration in early systole. The duration of the flow and of the acceleration phase can also be measured. Pre-ejection periods can be derived if an electrocardiographic signal is simultaneously recorded on the transcutaneous aortovelographic tracing.

The use of a triangular approximation to the actual waveform overestimates the area by some 10 to 25 per cent, but the error introduced is normally constant in any one subject. As the prime objective in these studies was to establish the degree of proportionality in any one patient between measures of flow obtained by transcutaneous aortovelography and by established techniques, this approximation introduced little error. Agreement with absolute values will however be affected.

Experimental procedure

The accuracy of this instrument was tested in 20 patients (15 men and 5 women), between the ages of 39 and 65 years, undergoing routine diagnostic cardiac catheterization for the investigation of ischaemic heart disease. Cardiac output was measured by an indicator dilution technique at rest and during atrial pacing at rates up to 160/min. A bolus of 10 mg indocyanine green was injected into the pulmonary artery and arterial blood was withdrawn from the femoral artery by a constant rate syringe through a cuvette densitometer[1] feeding a chart recorder. All cardiac output measurements were made in duplicate and stroke output was obtained by dividing the result by the heart rate during inscription of the curve. Transcutaneous aortovelographic observations of aortic velocity were made just after the indocyanine green injections at each heart rate. The stroke output was calculated from the product of the area under the velocity curve using the triangular approximation (the average of some 10 beats immediately after the injection was taken) and the cross-sectional area of the transverse aorta. The last was obtained from a lateral aortic root angiogram obtained at the end of the procedure. The diameter of the distal part of the aortic arch was measured from systolic films and corrected for magnification. Assuming a perfectly flat velocity profile in the arch of the aorta, this product should give volume flow into the descending aorta and therefore some 75 per cent of cardiac output, since the flow to the coronary arteries, head, neck, and upper limbs calculated from physiological data (Keele and Neil, 1971) accounts for approximately 25 per cent of the cardiac output.

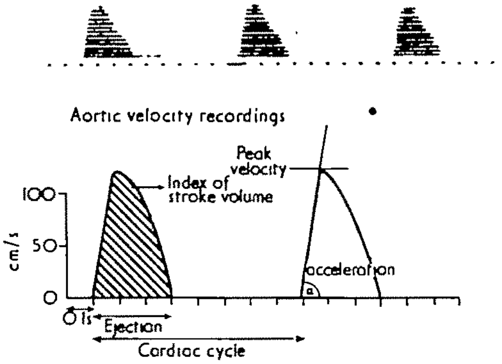

FIG. 4 *Drawings of the signals obtained by transcutaneous aortovelography indicate how the various measurements are extracted from the waveform. For the purpose of calculating the area under the curve, the waveform is treated as triangular. Mean velocity is obtained by dividing this area by the duration of the cardiac cycle. Acceleration is given by tan α.*

In 7 of these patients, after determination of cardiac output, an electromagnetic catheter tip velocity probe (Mills and Shillingford 1967) was introduced via the right femoral artery. The tip was positioned in the distal bend of the transverse aorta, the site of the transcutaneous aortovelographic observations, in the hope of obtaining the most closely comparable measure-

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[1] Gilford Instruments Ltd.

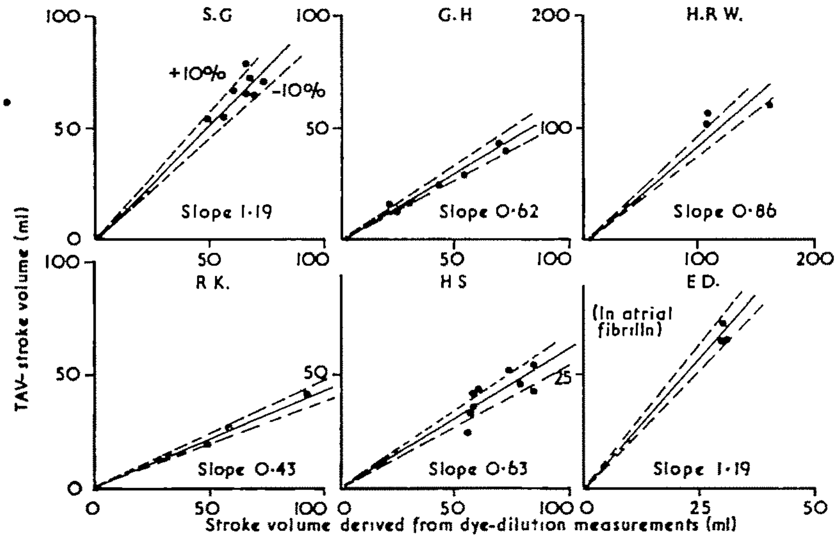

FIG. 5 *Correlations between stroke volumes in 6 patients, selected to show extremes of the spread found, as calculated from dye dilution measurements (plotted horizontally) and from transcutaneous aortovelographic readings together with angiographic measurements of an aortic diameter (plotted vertically). Pacing was used to vary the stroke volume. As no correction was made for the loss of flow to head, arms, and the coronary circulation, a slope of approximately 0·75 would be expected for the line of best fit (see text). Dashed lines indicate plus/minus 10 per cent variation from proportionality.*

ments. This, however, made it difficult to manoeuvre the catheter so that its tip was clear of the wall—in several subjects velocity readings differing by a factor of 4 to 1 could be obtained by manoeuvring the catheter tip.

The procedure adopted in the present studies was to place the tip so as to yield the highest stable readings which could be obtained without delaying the investigation. The peak velocities of individual beats were compared, except when nearly identical beats resulted from pacing at a fixed rate. Averages of 10 successive peaks were then compared. The level of the E-M trace in mid and late diastole was taken as zero (Gabe *et al.*, 1969).

Results

Stroke output

The result of these studies in 6 patients *selected to show the extremes that were encountered* is shown in Fig. 5. All show approximate proportionality, but major discrepancies in absolute values appear in several of the subjects as shown by the deviation of the observed slope of the 'best fit' line (visually drawn to pass through the origin) from the expected value of 0·75. The correlation points obtained in all subjects have been combined in Fig. 6 in such a way that the degree of proportionality found is clearly apparent. This has been achieved by adjusting the vertical scale of the individual studies so as to make all slopes equal to unity and then superimposing the results. The coefficient of variation (standard

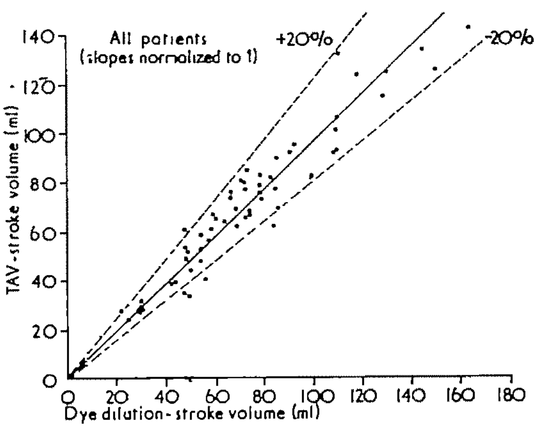

FIG. 6 *Pooled results from the patients in the series normalized so as to show the degree of proportionality in any one patient between transcutaneous aortovelography and dye dilution measures of stroke volume. Dashed lines indicate plus/minus 20 per cent deviation from exact proportionality.*

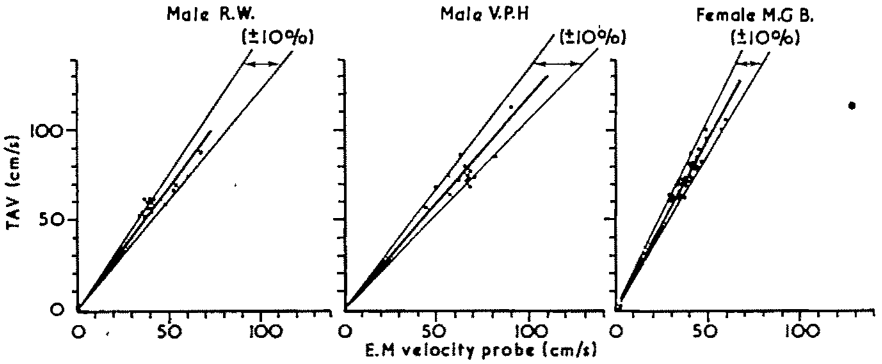

FIG. 7 *Correlation of peak velocity in 3 patients which illustrate the range of results found. Values obtained by transcutaneous aortovelography are plotted on the vertical axis while those obtained by an electromagnetic catheter tip velocity probe placed in the arch of the aorta are plotted horizontally. Plots (a) and (b) show results on two patients whose heart rate was varied by pacing. Patient (c) was in atrial fibrillation. The outer lines indicate plus/minus 10 per cent deviation from proportionality.*

deviation/mean), which is a measure of the departure of the observations from strict proportionality between the two techniques, was found to be 13 per cent.

Peak velocity

The results obtained in three studies, which illustrate the full spread in absolute values, is shown in Fig. 7. Good proportionality was found between the two techniques in all subjects. When the correlation points in the 7 patients (which included 2 in atrial fibrillation) were combined as above, the coefficient of variation was found to be 6 per cent.

Discussion

This technique is safe (power level less than 100 mW/cm^2) and convenient. Adequate signals can be obtained in 90 per cent of subjects. Because of its non-invasive nature, the investigation can be repeated as often as the state of the patient demands.

Proportionality with flow rate

The results of our experiments are encouraging and support the theoretical expectation that under most conditions there is good proportionality between the transcutaneous velocity readings obtained by this technique and the true flow rate. This suggests that transcutaneous aortovelography is capable of relative measurements (the quantification of changes) of velocity and flow in individual subjects. On average, there also was fair agreement on absolute values, but the error approached 2:1 in some subjects. The poor agreement on absolute values sometimes found is not surprising, since good agreement would only be expected if the velocity profile in the aortic arch were exactly flat. Errors in the evaluation of the transcutaneous aortovelographic records (triangular approximation), in the estimation of the cross-sectional area of the transverse aorta (radiographic magnification and assumption of circular cross-section), and in the approximation that 25 per cent of the cardiac output is distributed to the coronary arteries, head, neck, and upper limbs could contribute to the poor agreement of absolute values. We suspect, however, that departures from flatness of the flow profile and from circularity of cross-section are mainly responsible.

The observed proportionality between the mean transcutaneous aortovelographic velocity and cardiac output obtained by green dye suggests that in a given subject these factors remain relatively constant. While this will commonly be so, circumstances can be foreseen where they may vary substantially. Thus, compression of the aortic arch by a tumour might progressively change the velocity profile, while influences that selectively affect the cerebral circulation will modify the proportion of cardiac output entering the descending aorta (see Appendix). In other circumstances changes in systolic blood pressure may affect the cross-sectional area of the aorta, but data obtained by non-invasive techniques suggest that gross changes in pressure are required to give clinically significant changes in adults (Goldberg, 1971; Olson and Shelton, 1972).

In patients with aortic regurgitation, the systolic waveform normally displayed represents gross ejected stroke volume. It may prove possible to estimate the fraction of regurgitant flow by observing also the reverse flow velocities in the aorta, which can be seen on an alternative centre-zero display range (Light, 1974).

Velocity comparisons

The observed agreement between the velocity measurement obtained by transcutaneous aortovelography and the electromagnetic catheter tip velocity probe is satisfactory when the difference between the nature of the two measurements is borne in mind.

The electromagnetic velocity probe is an accurate method of measuring the velocity in the immediate vicinity of the catheter, provided this is roughly aligned (within <45°) with the direction of flow. Transcutaneous aortovelography, on the other hand, registers the highest velocity in the insonated portion of the arch. Agreement between the actual values recorded by the two techniques would, therefore, be expected only if the catheter tip were in the part of the cross-section carrying the highest velocity flow and fairly well aligned to its direction; otherwise the electromagnetic system should, as was indeed observed, give lower readings which, however, are proportional to those of transcutaneous aortovelography.

Flow profile

These studies also produced some evidence suggesting that the transverse flow profile in the aorta is remarkably little affected by irregularities in intracardiac haemodynamics. Thus, the departures from exact proportionality in a patient with atrial fibrillation (Fig. 7c) were no greater than those seen in the paced patients. Likewise the points representing the occasional ventricular extrasystoles in the paced patients (which are included in the plots of Fig. 7a and b) did not deviate in an obvious way from the pattern produced by regular beats. Whether this is consistently true of the whole range of aberrant or diskinetic ventricular contractions requires further study.

Specificity of measurement The above results by themselves do not prove that the transcutaneous aortovelographic measurement, i.e. the *outline* of the recorded signal, arises from aortic flow. Negative Doppler shifts will also be returned by the pulmonary artery or veins, which may well be within the beam. By virtue of the inclination to the ultrasonic beam, however, it is improbable that signals originating from the *pulmonary artery* would contain Doppler shifts high enough to contribute to the outline of the spectrum unless it was carrying flow of disproportionately high velocity.[1] Evidence which precludes interference to the outline from this source has been more fully reported elsewhere (Light, 1974):

1) The negligible effect of quite substantial variation of the direction of the transducer and hence of the ultrasonic beam on the signal outline indicates that the direction of flow is nearly in line with the beam.
2) The finding that in a patient with subvalvular stenosis the incidence of waveform abnormalities was identical in the transcutaneous aortovelographic recording and in that obtained from a catheter tip velocity probe in the ascending aorta.
3) In slow and deep respiration, the phase of the respiratory modulation observed was that appropriate to aortic blood flow but not that to pulmonary artery flow. Responses to Valsalva manoeuvres were similarly characteristic of aortic flow.
4) Further confirmation is afforded by observations in a proven case of atrial septal defect with a 4:1 shunt where, having obtained an aortic velocity waveform from the usual position, lowering the aim of the ultrasonic beam produced a different waveform from exceptionally fast pulmonary artery flow.

Such observations do not rule out the possibility that signals from the pulmonary artery can obscure the aortic velocity outline in an occasional subject and some vigilance is, therefore, still required.

Venous signals are commonly seen on transcutaneous aortovelographic tracings but normally give very low Doppler shifts which are easily distinguished from aortic signals. However, in certain conditions venous flow may be very pulsatile with resultant high peak velocities which could mimic aortic flow. Such venous waveforms are, however, characterized by substantial respiratory modulation and are readily differentiated from the coexisting aortic signal by their post-systolic timing. The transcutaneous aortovelographic display, in which signals from different vessels often register in different shades of grey, further helps in distinguishing such interference (Cross and Light, 1974).

[1] With the signal handling and presentation methods (spectral analysis and display) used in the non-invasive haemotachograph, the presence of even very powerful signals with relatively low Doppler shifts does not impair recognition of the wanted variable, which is the highest Doppler shift simultaneously present. The spectral presentation also often allows intersecting flow waveforms, as from venous flow, to be resolved. This is in contrast to single-line representations of the signal, particularly if these indicate an average of all the negative Doppler shifts present.

Other information obtainable

In addition to indices of flow, other variables of haemodynamic interest can be obtained from velocity measurements. The clinical value of observing peak velocity or the duration of the flow phase (Perloff and Reichek, 1972) or acceleration (Bennett *et al.*, 1974; Noble, Trenchard, and Guz, 1966) which can all be derived from the waveform obtained by transcutaneous aortovelography is as yet uncertain, though these measurements have recently aroused much interest (Mitchell and Wildenthal, 1972; Bos, 1972; Noble, 1972). These measurements or changes in them as a result of deliberate controlled stressing as by atrial pacing (Sowton *et al.*, 1967; Linhart, 1971) may give some indication of left ventricular function. In contrast to echocardiographic observations of segmental ventricular wall motion, which characterize local abnormalities (Gibson and Brown, 1974), transcutaneous aortovelography should give complementary information on overall left ventricular function.

Some factors relevant to the interpretation of blood velocity data are discussed by Light (1976), and the early results of a clinical evaluation are described by Buchtal, Hanson, and Peisach (1976).

Conclusion

We conclude that transcutaneous aortovelography is a useful non-invasive technique for following serial changes in stroke output and other indices of left ventricular function. The ability to assess, as often as desired, the response of a patient to a variety of therapeutic interventions should prove valuable in intensive care and coronary units. Transcutaneous aortovelographic measurements should similarly facilitate human studies into the inotropic and haemodynamic effect of drugs or anaesthetic agents which affect the circulation and in particular the time course of their action. The application of the technique for the measurement of absolute flow is ruled out until convenient non-invasive methods can be developed to measure the other factors discussed above which affect volume flow. The technique is capable of further refinement, and experience with it is still limited. Further use should allow us to define more clearly its scope of application in patient care and diagnosis.

APPENDIX

Relation between velocity, as observed by transcutaneous aortovelography, and measures of blood flow

If the transverse flow profile is exactly flat, the *area* (L) of the systolic complex (the darkened area) represents the length of the column taken up by the volume of blood which passes the measurement region in the corresponding heart beat.

The product of this area and the cross-sectional area of the transverse aorta (A) should give the part of the stroke volume entering the descending aorta. The full stroke volume (SV) will be given by

$$\mathrm{SV} = \mathrm{L.A.f.} \qquad \ldots\ldots(1)$$

where f=the ratio between flows in the ascending and descending aorta. Similarly, the above product, multiplied by heart rate (n), should give the cardiac output (CO)—

$$\mathrm{CO} = \mathrm{n.L.A.f.} \qquad \ldots\ldots(2)$$

Another—equivalent—expression for cardiac output is—

$$\mathrm{CO} = \bar{\mathrm{v}}.\mathrm{A.f.} \qquad \ldots\ldots(3)$$

where $\bar{v}$ is the time-average of the indicated blood velocity.

When, as will be the case in practice, the transverse flow profile is not perfectly flat, another factor, p, must be introduced:—

$$\mathrm{p} = \frac{\text{Average velocity throughout lumen}}{\text{Highest velocity in insonated region}}.$$

Equations (1) to (3) now become

$$\mathrm{SV} = \mathrm{L.A.f.p.} \qquad (1)$$

$$\mathrm{CO} = \mathrm{n.L.A.f.p.} \qquad (2)$$

$$\mathrm{CO} = \bar{\mathrm{v}}.\mathrm{A.f.p.} \qquad (3)$$

Exact proportionality in serial observations between velocities observed by transcutaneous aortovelography and flow rate into the descending aorta thus depend on two factors remaining constant in any one patient: the profile factor, p, and the cross-sectional area of the aorta, A.

As argued in the text, these two factors will be constant to a first approximation over a considerable range of conditions. This is also borne out by the results of the present study, in which stroke volumes (but not necessarily cardiac output) varied greatly.

Largely because of the autoregulation of the cerebral and coronary circulations, the factor, f, will fall with cardiac output when this is pathologically low. As a result, though transcutaneous aortovelography continues to present flow into the descending aorta with the accuracy to which p and A are constant, the sensitivity of the measurement to changes in cardiac output *increases* at low levels of the latter. Changes in cardiac output are thus more clearly apparent, though the accuracy with which they may be measured is decreased.

At pathologically low levels of cardiac output it is most appropriate to think of transcutaneous aortovelography as providing a measure of blood flow into the descending aorta. As this is also the flow available to perfuse the abdominal organs and the majority of the skeletal tissues, the variable thus indicated is one of importance to the patient's survival.

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Transcutaneous aortovelography
Potentially useful technique in management of critically ill patients

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Pilot evaluation of the clinical use of transcutaneous aortovelography has been undertaken and suggests that this technique will be useful in the assessment of left ventricular function in the acutely ill patient. Changes in waveform as a result of therapy or alteration in clinical condition can frequently be noted by critical visual assessment. Increasing clinical experience suggests that quantification will permit interpretation of less obvious changes in the recorded waveform. Transcutaneous aortovelography has the simplicity, speed, and safety afforded by a non-invasive technique.

The treatment of a critically ill patient necessitates the use of various measurements to serve as guide lines in patient management. These measurements should be reliable, easily obtainable, reproducible, and preferably non-invasive.

In the management of these patients a compromise has frequently to be reached between obtaining objective indices and initiating therapy based on clinical assessment. Rapid deterioration in the patient's condition may necessitate 'blind' therapy which, if inappropriate, may lead to further deterioration.

There is a need for a rapid, reliable technique for the repeated measurement of left ventricular output, so that changes in output can be observed. Transcutaneous aortovelography may meet this requirement. This preliminary report describes the use of this technique in an Intensive Therapy Unit.

Instrumentation and basic therapy

The instrumentation and basic principles of the technique have been described in the preceding paper (Sequeira *et al.*, 1976).

Method

The method is described in the preceding paper (Sequeira *et al.*, 1976). Clinical experience has shown that the transducer usually has to point downwards and to the left in order to align the ultrasonic beam with blood flow in the transverse arch of the aorta. The controls which are constantly used during recording—recorder on/off, display intensity, and an event marker—are on a small, hand-held, remote control box so that one person can conveniently operate the instrument (Fig. 1).

A reproducible recording could be obtained in approximately 90 per cent of patients. Difficulties arose in patients with pulmonary emphysema and in those who were restless or could not lie flat.

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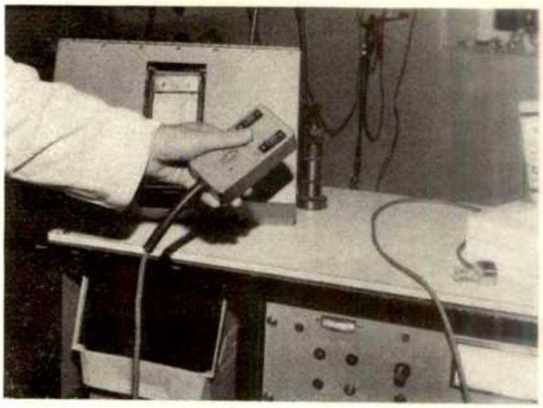

FIG. 1 *Hand-held remote control box used in conjunction with non-invasive haemotachograph (see Fig. 1 of Sequeira et al., 1976) for display of aortic velocity*

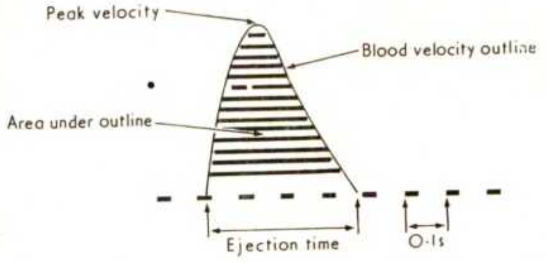

FIG. 2 *Visual assessment of transcutaneous aortovelograph recording*

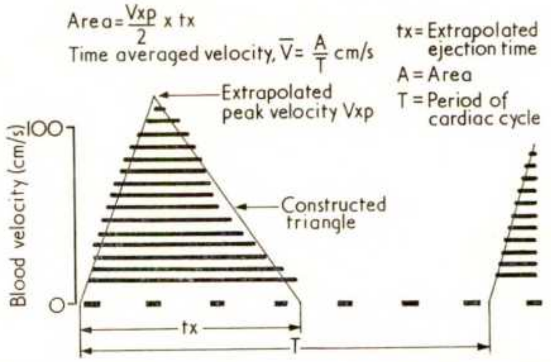
Area = $\frac{Vxp}{2}$ x tx
Time averaged velocity, $\bar{V} = \frac{A}{T}$ cm/s
tx = Extrapolated ejection time
A = Area
T = Period of cardiac cycle
Extrapolated peak velocity Vxp
Blood velocity (cm/s)
100
0
Constructed triangle
tx
T

FIG. 3 *Quantitative analysis of transcutaneous aortovelograph recording*

Records cannot be obtained from patients with tracheostomies or patients with surgical emphysema of the neck.

Interpretation

The outline of the aortic blood velocity signal describes the highest Doppler shifts received at any time, corresponding to the maximum aortic blood velocity. Even if other vessels are within the beam, no vessel in this area normally contains receding blood flowing with such high velocities in a direction so closely aligned with the ultrasonic beam. Venous signals can usually be readily distinguished by their low Doppler shifts and diastolic timing.

Changes in the volume flow entering the descending aorta can be calculated from changes in maximum aortic velocities on the assumptions that the cross-sectional area of the vessel, its velocity profile, and the proportion of blood supplying the head, upper limbs, and coronary arteries (all of which is lost to measurement) remains constant between observations. Initially we found that visual assessment of the record gave useful sequential information (Fig. 2), but a quantitative analysis of the records is now being made to facilitate interpretation of less obvious waveform changes (Fig. 3). By fitting straight lines to the leading and trailing edges of the record, several measurements can be made. The height (Vxp) of the constructed triangle measures peak velocity, and the length of the base (tx) of the triangle ejection time. The area (A) gives an index of stroke volume, and the quantity $\bar{V}$ is the time-averaged or mean maximum velocity and is expressed in cm/s. Fig. 3 shows how these calculations are made. When respiratory variations are present, the record is analysed over a number of respiratory cycles. So far, these calculations have been made in a few patients only.

Subjects studied

Over a period of 4 months recordings were obtained from 68 subjects, 21 of whom were healthy volunteers. A total of 47 patients were studied (Table).

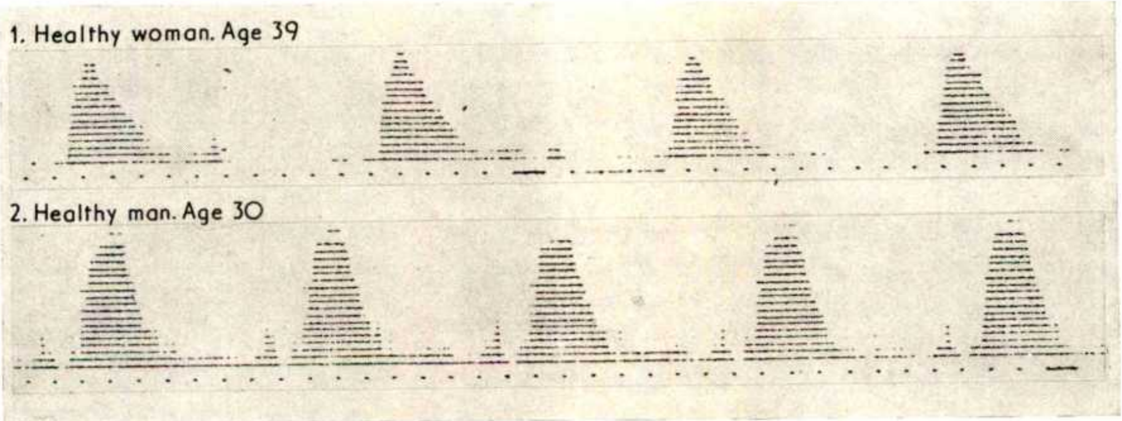

FIG. 4 *Transcutaneous aortovelograph recordings obtained from normal subjects*

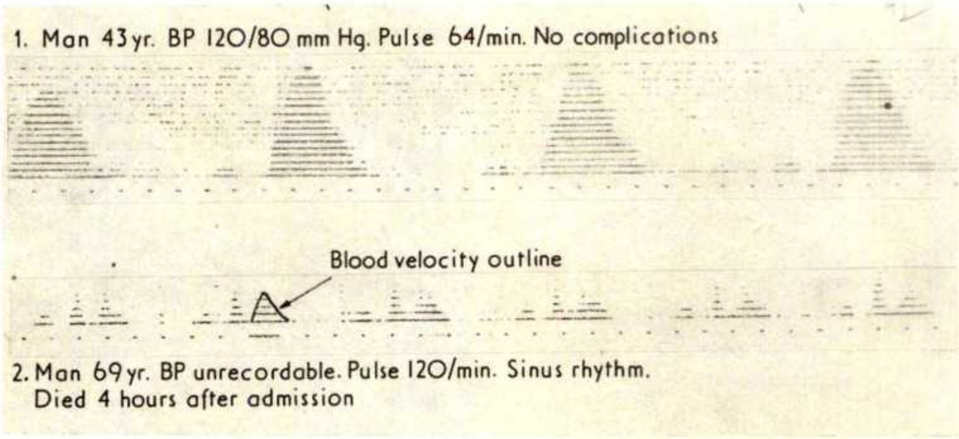
1. Man 43 yr. BP 120/80 mm Hg. Pulse 64/min. No complications
Blood velocity outline
2. Man 69 yr. BP unrecordable. Pulse 120/min. Sinus rhythm. Died 4 hours after admission

FIG. 5 *Myocardial infarction. Transcutaneous aortovelograph recordings in two patients on admission to hospital*

TABLE *Patients studied*

Category		*No. of patients studied*
Myocardial infarction		21
'Shock'	Hypovolaemic	6
	Septic	7
Drug overdose		5
Drug response		3
Miscellaneous		5

Results

Normal subjects

Records obtained from the 21 healthy subjects gave some impression of the range of normal appearances (Fig. 4). Clearly more subjects are required in order to assess the range of normal values obtained and their statistical distribution. In our initial study we were primarily concerned with analysis of sequential changes in the same patient and not with comparison of data between different patients.

Myocardial infarction

All 21 patients studied had electrocardiographic evidence of a recent myocardial infarction. Patients with no clinical evidence of myocardial dysfunction other than a fourth heart sound had transcutaneous aortovelography records which were not obviously abnormal. Clinical evidence of deterioration in

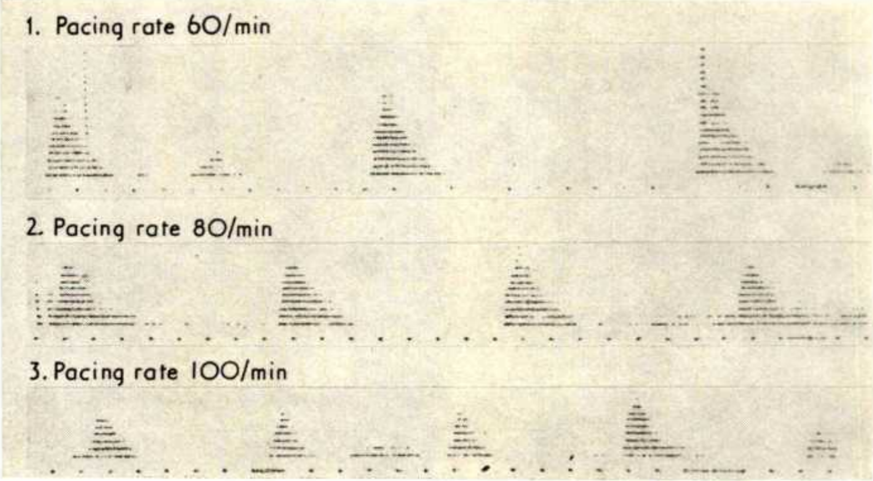

FIG. 6 *Transcutaneous aortovelograph recordings in a patient with complete heart block showing effect of endocardial pacing at different rates*

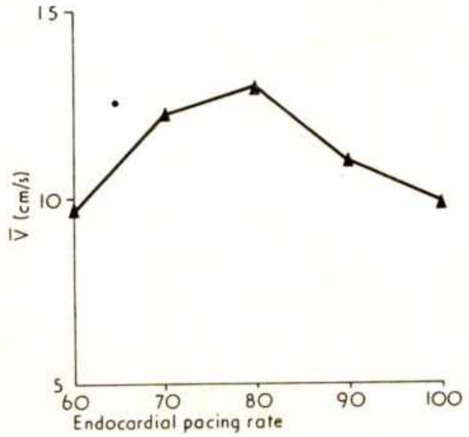

FIG. 7 *Effect of endocardial pacing at different rates on time-averaged mean velocity calculated from recordings in Fig. 6*

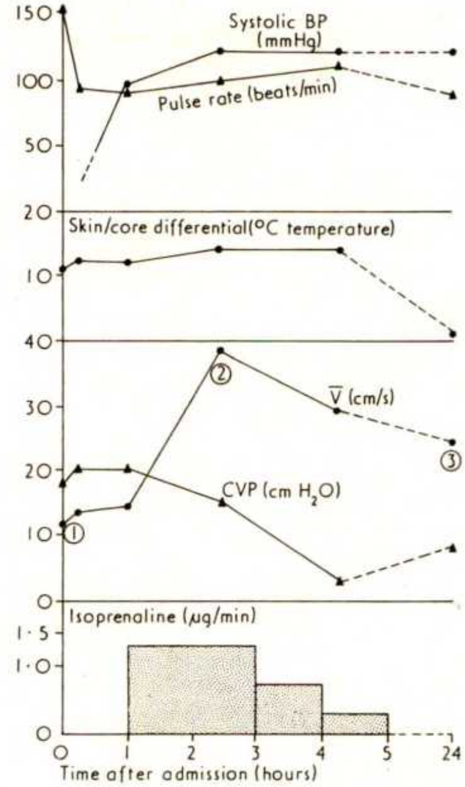

FIG. 9 *Observations, including time averaged mean velocity ($\bar{V}$), obtained from patient admitted with hypovolaemic shock (numbers on graph of $\bar{V}$ refer to transcutaneous aortovelograph traces shown in Fig. 8)* →

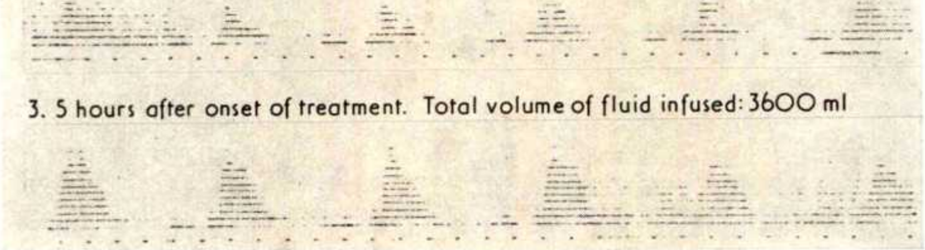
1. Before treatment
2. I hour 45 minutes later
3. 5 hours after onset of treatment. Total volume of fluid infused: 3600 ml

FIG. 8 *Sequential transcutaneous aortovelograph recordings taken from a patient with hypovolaemic shock and treated by volume replacement*

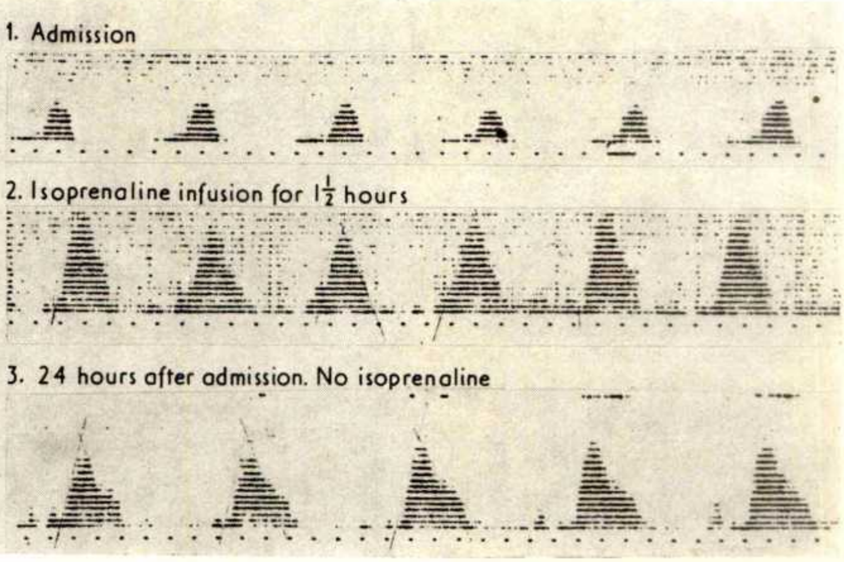
1. Admission
2. Isoprenaline infusion for $1\frac{1}{2}$ hours
3. 24 hours after admission. No isoprenaline

FIG. 10 *Sequential transcutaneous aortovelograph recordings taken from patient admitted with amylobarbitone overdose*

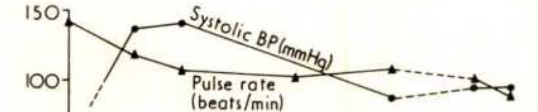

FIG. 11 *Amylobarbitone overdose. Graph showing progress and response to therapy (numbers on graph of $\bar{V}$ refer to transcutaneous aortovelograph traces shown in Fig. 10)*

cardiac output (a falling blood pressure, tachycardia, and peripheral vasoconstriction) was associated with a record showing a reduced peak and mean velocity and shortened ejection time (Fig. 5). Clinical improvement in cardiovascular status was also associated with signs of improvement in the transcutaneous aortovelogram, shown by rising peak velocity and longer ejection time. Further study is clearly required in order to establish whether transcutaneous aortovelography might be of value in the initial haemodynamic assessment of patients admitted with acute myocardial infarction and whether changes in sequential recordings might give a guide to prognosis.

Complete heart block associated with myocardial infarction

Two patients were admitted with complete heart block. Transcutaneous aortovelograph recordings obtained at different pacing rates in one of these patients are shown in Fig. 6. The results are presented by plotting the endocardial pacing rate against the mean velocity ($\bar{V}$) (Fig. 7). The mean velocity was found to be maximum at a pacing rate of 80/min. Measurements made from transcutaneous aortovelograph recordings at different heart rates in patients paced endocardially may make it possible to select the optimum pacing rate for that individual.

'Shock'

Serial recordings were obtained in shocked patients from the time of admission to the Intensive Therapy Unit; additional records were made when a drug or manoeuvre was expected to affect the haemodynamic status of the patient. Whenever possible appearances were interpreted in the light of changes in pulse rate, blood pressure, central venous pressure, urine output, and skin-core temperature differences.

Hypovolaemic shock

Recordings from patients admitted in hypovolaemic shock consistently showed a low peak and mean velocity, short ejection time, and small area. Fig. 8 shows the sequential changes in transcutaneous aortovelograph recordings from a patient admitted with shock and treated by fluid replacement. Fig. 9 shows the various observations made during the treatment of shock. The systolic blood pressure was unrecordable on admission and the mean velocity recorded by transcutaneous aortovelography was extremely low. Fluid therapy (combination of purified protein fraction and crystalloids) was begun on the basis of these findings and of evidence of fluid loss over the previous week. A central venous pressure line was not established until an hour later, but the measured central venous pressure was then less than zero (mid-thorax reference level) after intravenous infusion 800 ml in one hour. With increasing volumes of fluid infused, there was a steady increase in mean aortic velocity, central venous pressure, and blood pressure; the skin-core temperature difference decreased as peripheral perfusion improved. Records from patients with myocardial failure showed a similar appearance to those from patients in hypovolaemic shock, but these patients usually had a raised central venous pressure and did not show improvement after a fluid challenge. On the other hand, mean aortic velocity rapidly increased with a fluid challenge in hypovolaemic patients and this was associated with a simultaneous increase in central venous pressure.

Septic shock

In this condition, transcutaneous aortovelograph appearances are variable. Interpretation of these records will require detailed measurements and correlation with other cardiovascular indices in order to determine whether the technique will prove of value in the management of this condition.

Drug overdose and drug response

Fig. 10 shows sequential transcutaneous aortovelograph recordings taken from a patient admitted with an amylobarbitone overdose. Fig. 11 shows the various observations made. At the time of admission, the central venous pressure was high, the pulse rate was 150/min, and the blood pressure unrecordable. The mean aortic blood velocity was low. These findings were consistent with the diagnosis of 'shock' secondary to a fall in cardiac output, presumably a result of the myocardial suppressant effect of amylobarbitone. In view of these changes an isoprenaline infusion was started. This was followed by a fall in the central venous pressure, a rising blood pressure, a steady increase in urine output, and a dramatic increase in the mean aortic blood velocity. It was possible to regulate the dosage of isoprenaline infused in order to maintain an improved but submaximal mean velocity and a pulse rate of 110/min or less.

Conclusion

Our limited experience suggests that sequential transcutaneous aortovelograph recordings in conjunction with other clinical indices may be of value in the management of hypovolaemic shock and response to fluid therapy, and as an indicator of the effect of a drug on the cardiovascular system. They may also prove to be of particular value in the assessment of the therapeutic effect of inotropic agents and agents producing peripheral vasodilatation, so that a titrated dose can then be administered intravenously.

Transcutaneous aortovelography has the advantage over many other techniques for assessment of cardiovascular function being non-invasive. Recordings can be obtained from approximately 90 per cent of critically ill patients and sequential observations made with little patient discomfort. A pilot evaluation suggests that this technique provides useful information on cardiovascular status, and that serial records can give a guide to progress and response to therapy. Simple quantitative analysis of the tracings is likely to increase their value.

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British Heart Journal, 1976, **38**, 457-464.

Association of ventricular extrasystoles and ventricular tachycardia with idioventricular rhythm

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Patients with acute myocardial infarction were monitored for ventricular arrhythmias in the first 48 hours.

Idioventricular rhythm (rate less than 100/minute) occurred in 35 out of 224 patients (15·6%) during the first day and in 13 out of 192 patients not receiving treatment on the second day (6·8%). This arrhythmia was frequently preceded by late ventricular extrasystoles, which often showed variation of their coupling intervals to the preceding QRS. Double ventricular extrasystoles separated by ≥600 ms were also precursors of idioventricular rhythm. Idioventricular rhythm at times could be described as an escape rhythm, but on other occasions it was undoubtedly an accelerated rhythm. Spontaneous changes in the idioventricular cycle length were frequent on single one-minute electrocardiographic recordings. The rate of the dominant rhythm in patients with episodes of idioventricular rhythm was significantly slower than the heart rate of patients without this arrhythmia. Idioventricular rhythm was more frequent in patients with inferior infarction.

Idioventricular rhythm sometimes preceded ventricular tachycardia but there was only a significant association between ventricular tachycardia and idioventricular rhythms with rates of over 75/minute. Irregular idioventricular rhythm frequently accelerated to ventricular tachycardia. It is suggested that the term benign idioventricular rhythm be reserved for those rhythms below 75/minute, and that the term rapid idioventricular rhythm should be used for rhythms between 75 and 120/minute. The rate of idioventricular rhythm is related to the probability of development of life-threatening ventricular arrhythmias during the first 48 hours after myocardial infarction.

Idioventricular rhythm and ventricular tachycardia are not clearly separated in many early analyses of the arrhythmias occurring after acute myocardial infarction (Julian, Valentine, and Miller, 1964; Fluck *et al.*, 1967; Lawrie *et al.*, 1968). However, subsequently it has been found that slow ventricular rhythms are more benign than faster rhythms (Rothfield *et al.*, 1968; Norris, Mercer, and Yeates, 1970). Many idioventricular rhythms are critically dependent on the underlying heart rate, appearing when this slows and disappearing when the sinus rhythm accelerates. The terms 'slow' and 'benign' idioventricular rhythm have become popular. Though the extremes of rate of idioventricular rhythm and ventricular tachycardia do justify such a distinction, it is not easy to provide a definition of these arrhythmias that not only separates their electrocardiographic features but also their clinical significance. Therefore, the dividing line between these arrhythmias has been variously drawn at 100 to 120 beats a minute (Rothfield *et al.*, 1968; Norris *et al.*, 1970; De Soyza *et al.*, 1974a).

In this study the importance of these 'slow' ventricular rhythms after acute myocardial infarction and their relations with ventricular tachycardia and measures of ventricular extrasystolic activity have been examined.

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Patients and methods

Between January 1974 and November 1974 269 patients with acute myocardial infarction were admitted to the coronary care unit of the Sheffield Royal Infirmary: 31 patients died in cardiogenic shock during the first 48 hours after myocardial infarction, and 5 patients were paced within 6 hours of admission because of complete heart block. These and a further 9 patients who were on antiarrhythmic therapy on admission were excluded from the study. The remaining 224 patients formed the subject of this study.

The patients were monitored continuously by the nursing staff for at least 48 hours and electrocardiographic recordings were taken of any episodes of idioventricular rhythm or ventricular tachycardia. The nursing staff recorded the number of ventricular extrasystoles at hourly intervals. If at these times the number of ventricular extrasystoles was ≥ 5/minute a one-minute electrocardiographic recording was taken and this was repeated at 6-hourly intervals for 48 hours. Similar observations were made at other times if ventricular extrasystoles appeared or increased in number.

A clinical assessment of each patient was made on admission and at least daily thereafter throughout the patient's stay in hospital. Daily 12-lead electrocardiograms and at least one chest radiograph were performed in the first 48 hours.

Antiarrhythmic therapy was not used routinely but was given for ventricular tachycardia or after an episode of ventricular fibrillation. An episode of ventricular tachycardia was diagnosed when there were three or more ventricular extrasystoles in a row separated from each other on average by <600 ms. The cycle length of each arrhythmia was measured and idioventricular rhythm was considered irregular if the range of variation of cycle length was greater than 10 per cent of the mean cycle length.

The diagnosis of ventricular extrasystoles and their differentiation from aberrant conduction were based on the usual electrocardiographic criteria (Lipman and Massie, 1965; Sandler and Marriott, 1965; Talbot, 1973). All the coupling intervals of single uniform ventricular extrasystoles on each record were examined. If there were multiform ventricular extrasystoles the coupling intervals of each form of extrasystole were measured separately. Uniform ventricular extrasystoles which had more than 100 ms variation in their coupling intervals were described as variable coupled extrasystoles. All recordings were examined for parasystole (Scherf and Schott, 1953). Ventricular extrasystoles that occurred on or after the P wave of the succeeding sinus beat have been called late ventricular extrasystoles. Two successive extrasystoles separated from each other by ≥ 600 ms and ventricular bigeminy lasting for at least a minute were recorded separately.

The diagnosis of myocardial infarction was made electrocardiographically and confirmed by serum enzyme tests (Blackburn *et al.*, 1960; Goldberg and Winfield, 1972). The location of infarction was described as anterior, inferior, septal, or lateral or any combination of these (Talbot *et al.*, 1973). The time of onset of infarction was determined from the clinical history and examination in conjunction with the results of three serum enzyme tests on consecutive days. If these were conflicting a further history was taken to elucidate if and when one or more infarctions had occurred.

Results

On the first day after infarction 35 out of 224 patients had one or more episodes of idioventricular rhythm. Thirty-two patients received treatment for ventricular tachycardia or ventricular fibrillation and, therefore, on the second day only 192 patients could be studied further. Nine of these patients had one or more episodes of idioventricular rhythm in the second 24 hours after infarction. In all, 44 patients had idioventricular rhythm. Seventeen of these patients also had ventricular tachycardia. In 12 patients idioventricular rhythm clearly preceded ventricular tachycardia, whereas in 5 patients idioventricular rhythm was interspersed with episodes of ventricular tachycardia and the initial arrhythmia could not be determined. Forty-two patients developed ventricular tachycardia during the 48-hour period. There was a significant association between idioventricular rhythm and subsequent episodes of ventricular tachycardia (χ^2 17·1, $P<0{\cdot}01$). There was also an association between episodes of ventricular tachycardia and idioventricular rhythm in single one-minute electrocardiographic recordings.

It was discovered that the association between idioventricular rhythm and ventricular tachycardia was the result of an association of faster irregular idioventricular rhythms between 75 and 100 per minute and ventricular tachycardia (Table 1). In this table the average cycle length and the variability of idioventricular rhythm with or without ventricular tachycardia are shown. Though arbitrary distinctions between these arrhythmias have been used in this paper, idioventricular rhythms and ventricular tachycardias were difficult to distinguish, since either rhythm could often end with cycles that were longer or shorter than the predominant cycle of the rhythm. In any individual patient the contour of the two rhythms was often similar, and they were often associated with ventricular extrasystoles of similar shape.

The average heart rate of the patients with idioventricular rhythm was 69·9 per minute (SD 13·9) and this was significantly slower than the average heart rate of patients without this arrhythmia on the first day after infarction (78·4 SD 15·2—$t=3{\cdot}3$, $P<0{\cdot}01$). Idioventricular rhythm was associated with inferior infarction. There were 88 patients with inferior infarction (37·7%), and of these, 21 had at least one episode of idioventricular rhythm. However, there were 136 patients with infarction in areas other than the inferior wall of the heart and of these only 14 had idioventricular rhythm ($\chi^2=6{\cdot}4$, $P<0{\cdot}05$). It appeared that the association of idioventricular rhythm and inferior infarction was the result of a parallel association with bradycardia, because there was no association of any ventricular rhythms with the site of infarction if only patients with heart rates between 75 and 100 a minute were considered.

Ventricular extrasystoles which preceded idio-

TABLE 1 *Association of idioventricular rhythm and ventricular tachycardia*

Idioventricular rhythm associated with ventricular tachycardia		*Idioventricular rhythm unassociated with ventricular tachycardia*	
Cycle length (ms)	*Variation of cycle and form*	*Cycle length (ms)*	*Variation of cycle and form*
700	—	1000	—
900	Irregular	1000	—
740	Irregular	1080	—
680	—	1200	—
900	Irregular	880	—
640	Irregular	920	Irregular/multiform
720	Multiform	960	Multiform
800	Irregular/multiform	1040	—
800	Irregular/multiform	800	—
800	Irregular/multiform	920	Irregular/multiform
900	Irregular/multiform	1020	—
780	—	960	—
640	Irregular	1200	—
660	—	960	Irregular/multiform
760	Irregular/multiform	1000	—
680	Irregular/multiform	1100	—
880	Irregular	1020	—
		840	Irregular/multiform
		940	—
		820	Irregular/multiform
		880	—
		980	Irregular
		1040	—
		1100	—
		1120	—
		1080	—
		1040	—
Mean cycle 764* (SD 92)		Mean cycle 996* (SD 109)	

*Significant difference ($t=7\cdot25$, $P<0\cdot01$).

ventricular rhythm showed a number of characteristic features (Table 2). Late ventricular extrasystoles were the most frequent precursors of idioventricular rhythm (Fig. 1, 2, and 3). These extrasystoles could have fixed coupling intervals but often they had variable coupling intervals, particularly in association with faster and irregular idioventricular rhythms.

The variation of coupling intervals was often, but not always, restricted to the end of electrical diastole (Fig. 2 and 3). Idioventricular rhythm associated with ventricular tachycardia was more often followed or preceded by ventricular extrasystoles which varied throughout electrical diastole. However, if the rate of the dominant rhythm was rapid, electrical diastole was so reduced that even 'late' ventricular extrasystoles were also close to the T wave. In such cases, though variation of coupling intervals was often obvious, such extrasystoles have to be described on the criteria used earlier as having fixed coupling (Fig. 4). Extrasystoles which occurred after a long sinus pause (escape beats) were also associated with idioventricular rhythm and late ventricular extrasystoles. The pauses could be the result of sinus arrhythmia, atrial extrasystoles, or sinus slowing after one ventricular extrasystole (Fig. 4).

Double ventricular extrasystoles, separated by more than 600 ms were associated with idioventricular rhythm (Fig. 2 and 3). Ventricular bigeminy occurred both before and after idioventricular rhythm. After lignocaine therapy for ventricular tachycardia, the rhythm was sometimes converted to idioventricular rhythm before it finally disappeared or changed to ventricular bigeminy.

Fusion beats were obvious in 15 patients with idioventricular rhythm (Fig. 2), but were also found alone or in association with variable coupling, double ventricular extrasystoles, and late ventricular extrasystoles. Parasystole was detected in two one-minute electrocardiographic recordings, but only one of the two patients had idioventricular rhythm. However, short episodes which could have been interpreted as parasystole or parasystolic ventricular tachycardia were often preceded by or followed unprotected idioventricular rhythm.

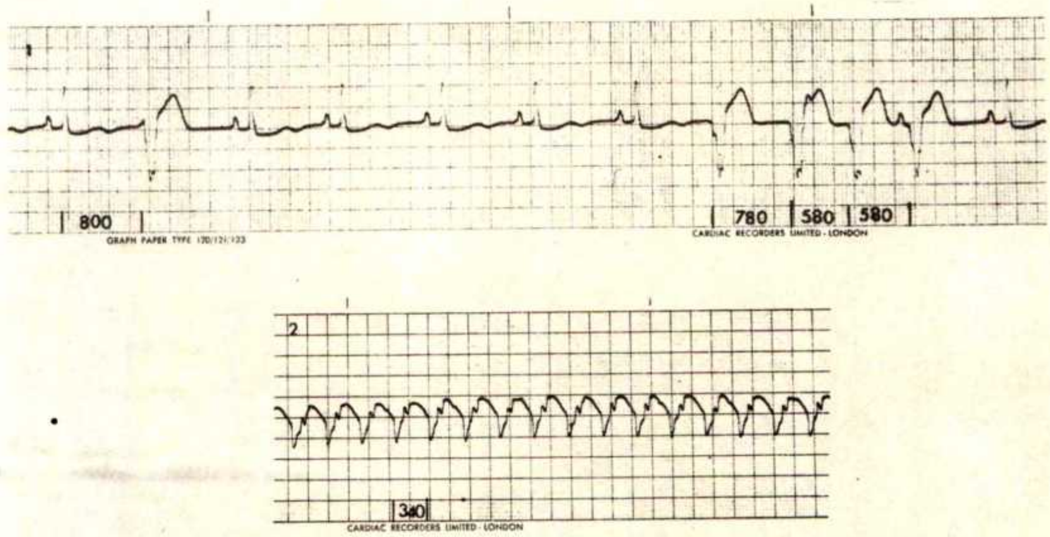
800
780
580
580
CARDIAC RECORDERS LIMITED · LONDON
2
340
CARDIAC RECORDERS LIMITED · LONDON

FIG. 1 *Top: One ventricular extrasystole towards end of electrical diastole. One episode of irregular idioventricular rhythm (mean cycle 630 ms). Bottom: Sustained ventricular tachycardia (cycle 340 ms).*

Discussion

This study has shown that idioventricular rhythm and ventricular tachycardia are associated. A clear distinction between these arrhythmias is impossible and many ventricular rhythms vary above and below 100/minute. Idioventricular rhythm sometimes follows paroxysms of ventricular tachycardia if these are not treated. By not treating idioventricular rhythm routinely, this arrhythmia was found to be a significant prelude to ventricular tachycardia. Idioventricular rhythm was associated with sinus rates below 75 a minute, and it appeared that this was the reason for an association with inferior infarction which is more often accompanied by sinus bradycardia than infarction in other areas of the heart. Idioventricular rhythms under such conditions were usually slower and not significantly associated with ventricular tachycardia. However, faster and irregular idioventricular rhythms of between 75 and 100 a minute were associated with ventricular tachycardia.

Idioventricular rhythm has been described as a distinct arrhythmia after myocardial infarction (Rothfield *et al.*, 1968; Norris *et al.*, 1970). It was soon appreciated that it was common and occurred in up to 30 per cent of patients. It did not appear as sinister as ventricular tachycardia, and was called benign. This is a relative term and recently it has been suggested that idioventricular rhythm and late ventricular extrasystoles can be a prelude to ventricular tachycardia (De Soyza *et al.*, 1974a, b). This study supports this view.

It is generally accepted that idioventricular rhythm is caused by increased ventricular automaticity. A number of features support this.

(1) It is associated with escape beats.

(2) Often the first ventricular extrasystole follows the preceding sinus beat by an interval that is

similar to or longer than the cycle of the idioventricular rhythm.

(3) It may be suppressed by acceleration of the dominant rhythm.
(4) It may be associated with fusion beats.
(5) It is usually unifocal and is sometimes associated with parasystole (Chung, Walsh, and Massie, 1965; Roelandt and Schamroth, 1971).

The original description of idioventricular rhythm only included accelerated ventricular rhythms that became manifest when the dominant rhythm slowed and could be abolished by acceleration of the sinus rate. Such an automatic focus cannot be protected and the rhythm is comparable to an escape rhythm in a patient with heart block.

However, the lack of protection may not be absolute even in a one-minute recording, so that parts of the rhythm may resemble parasystolic ventricular tachycardia (Chung *et al.,* 1965). If an exit block occurs intermittently, parasystole may be associated with idioventricular rhythm. Unequivocal parasystole is uncommon after acute myocardial infarction and appears to be benign. Protection of an ectopic focus does not appear to be related to the probability of ventricular tachycardia (Baxter and McGuinness, 1974), and in this study there was no evidence that episodes of idioventricular rhythm were a result of a regular exit block of ventricular tachycardia.

Parasystole and extrasystoles have features in common; they may not be easily distinguished and could be caused by similar local electrophysiological events (Watanabe, Pamintuan, and Dreifus, 1973; Watanabe, 1971). However, they could still be the result of enhanced automaticity and re-entry, respectively. Likewise, the relation between idioventricular rhythm and ventricular tachycardia does not prove that these arrhythmias are the result of the same mechanism. Variable coupled extrasystoles may be non-parasystolic and are associated

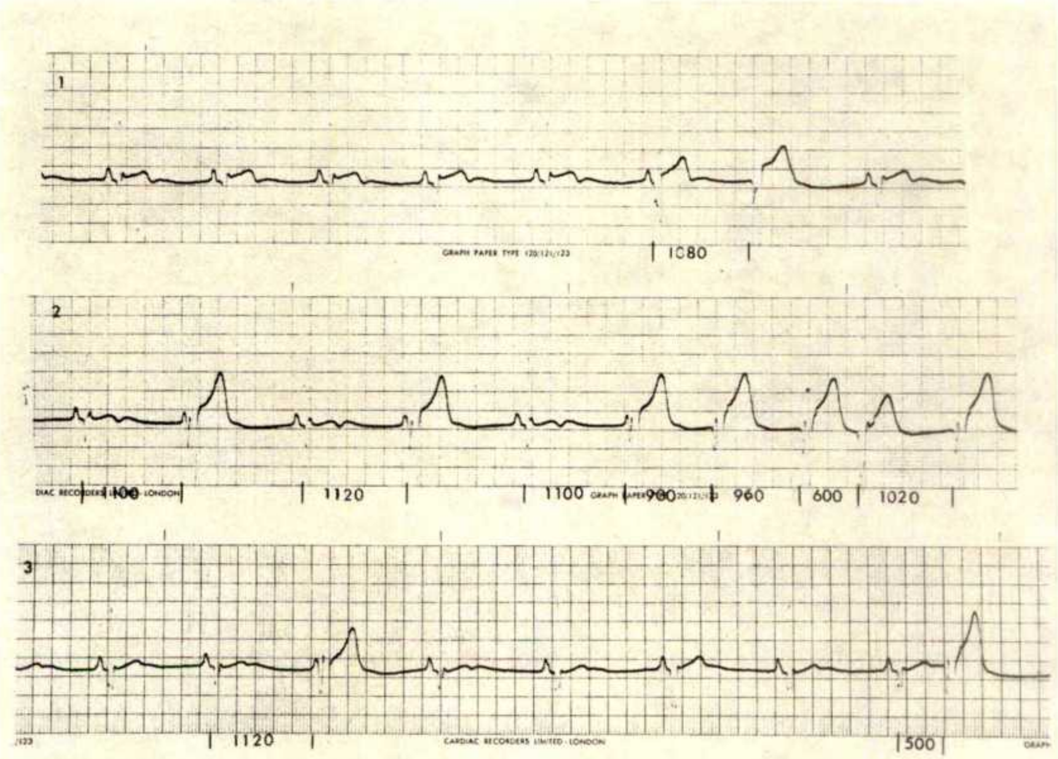

FIG. 2 *Top: Double ventricular extrasystoles (separated by 1080 ms). First extrasystole is late ventricular extrasystole. Middle: Two late ventricular extrasystoles associated with variable idioventricular rhythm. Bottom: Late ventricular extrasystole and possible fusion beat. One early ventricular extrasystole (variable coupling).*

TABLE 2 *Features of ventricular extrasystoles associated with idioventricular rhythm*

	No. of patients with idioventricular rhythm	*No. of patients without idioventricular rhythm*	*Total no. of patients*
Late ventricular extrasystoles	25*	16*	41
Variable coupling of ventricular extrasystoles	23*	31*	54
(a) $<80\%$ of electrical diastole	14*	24*	38
(b) $\geq 80\%$ of electrical diastole	9**	7**	16
Double ventricular extrasystoles (≥ 600 ms)	10**	5**	15
Ventricular bigeminy	12**	19**	31
Total no.	44	180	224

*Significant differences between patients with and without idioventricular rhythm (χ^2 test $P<0{\cdot}01$).
**Significant differences between patients with and without idioventricular rhythm (χ^2 test $P<0{\cdot}05$).

with ventricular tachycardia both in patients with chronic ischaemic heart disease and patients with myocardial infarction (Talbot, 1973; Talbot and Dreifus, 1975). The variable coupling associated with idioventricular rhythm is mainly related to late ventricular extrasystoles, but variable coupling related to ventricular tachycardia often extends closer to the T wave. If ventricular tachycardia is caused by re-entry, re-entry pathways may vary and this may be the explanation for the variable coupling of associated ventricular extrasystoles. There is also evidence that ventricular tachycardias may not be a homogeneous group of arrhythmias. Immediately after infarction they may be brought about by

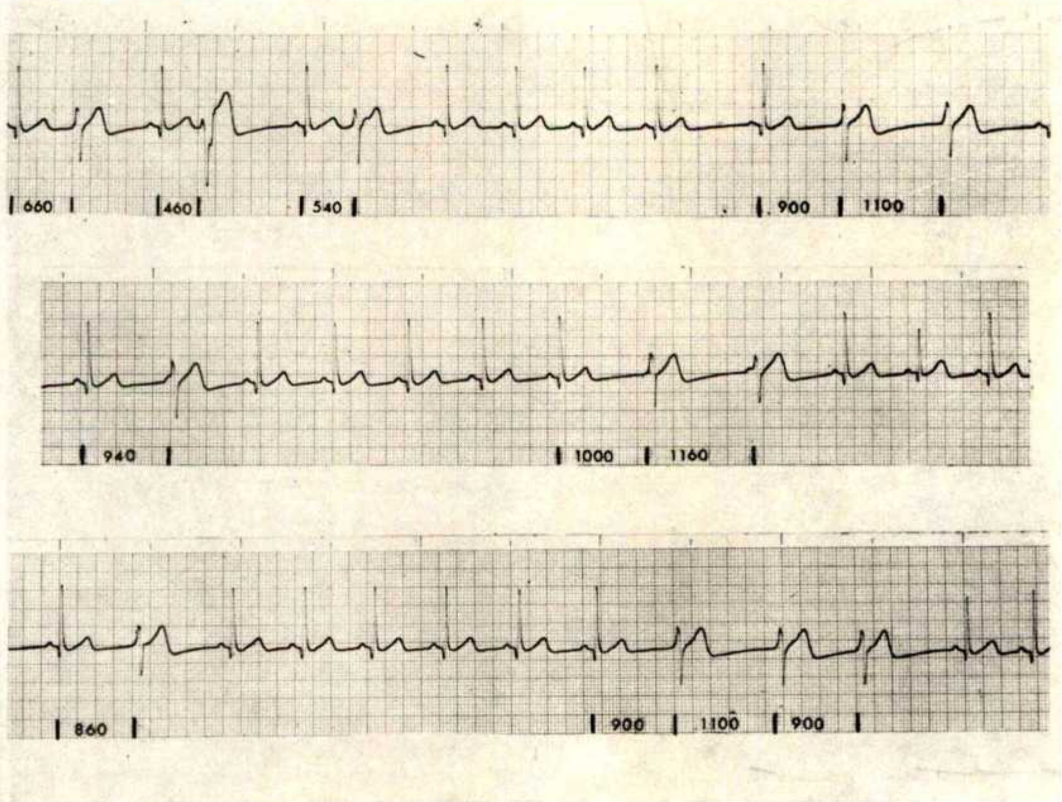

FIG. 3 *One-minute electrocardiographic recording showing variable coupling, double ventricular extrasystoles, late ventricular extrasystoles, and irregular idioventricular rhythm. The second ventricular extrasystole is slightly deformed because of prematurity.*

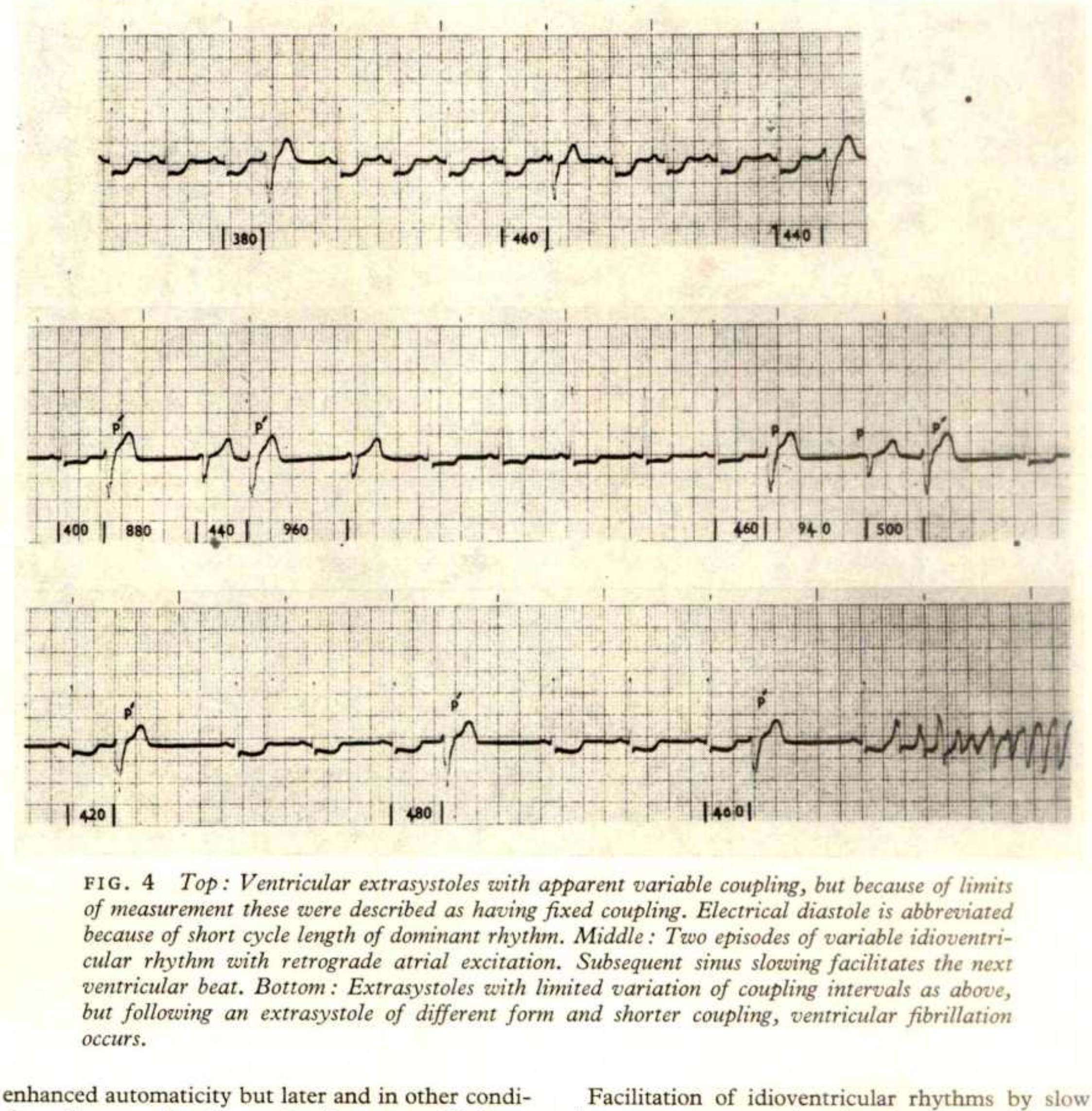

FIG. 4 *Top: Ventricular extrasystoles with apparent variable coupling, but because of limits of measurement these were described as having fixed coupling. Electrical diastole is abbreviated because of short cycle length of dominant rhythm. Middle: Two episodes of variable idioventricular rhythm with retrograde atrial excitation. Subsequent sinus slowing facilitates the next ventricular beat. Bottom: Extrasystoles with limited variation of coupling intervals as above, but following an extrasystole of different form and shorter coupling, ventricular fibrillation occurs.*

enhanced automaticity but later and in other conditions they may be the result of re-entry (Wellens, Lie, and Durrer, 1974).

The association of idioventricular rhythm and ventricular escape beats with late ventricular extrasystoles and double ventricular extrasystoles separated by $\geq$600 ms suggests that such extrasystoles are the result of increased automaticity. Since the coupling intervals of these extrasystoles often resemble that of the idioventricular rhythm, the ventricular focus is probably discharged by each sinus beat; however, perhaps because of varying automaticity or exit block, these extrasystoles are not always manifest.

Facilitation of idioventricular rhythms by slow sinus rates may explain why the slower idioventricular rhythms are of less significance. If automaticity is increased to such an extent that the rhythm is manifest at faster heart rates it must be a faster rhythm. Therefore, late ventricular extrasystoles at faster heart rates may be of more significance than those at slower heart rates (Fig. 4). In addition, ventricular extrasystoles which appear at variable times towards the end of electrical diastole will more often be manifest and not dependent on sinus slowing.

It may be helpful to distinguish those rhythms that only become manifest with sinus slowing as benign or slow idioventricular rhythms (< 75/minute), and use the term rapid idioventricular rhythm for rhythms above this. The term ventricular tachycardia is well established for rhythms of 120/minute or over. Treatment may differ for slow and rapid idioventricular rhythms. Atropine may eliminate those arrhythmias associated with sinus slowing, but lignocaine may be a better treatment for those arrhythmias associated with a sinus rate of over 75/minute.

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British Heart Journal, 1976, 38, 465–471.

Incidence of arrhythmias induced by isometric and dynamic exercise[1]

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The incidence of arrhythmias during isometric sustained handgrip exercise and during dynamic graded bicycle exercise was compared in a group of 45 patients with various forms of heart disease on no antiarrhythmic therapy. Atrial arrhythmias were equally common during handgrip and bicycle exercise but ventricular arrhythmias were more frequent during handgrip exercise. Of the 45 patients, 38 per cent developed ventricular arrhythmias during isometric exercise, with ventricular tachycardia occurring in 15 per cent. During dynamic exercise 22 per cent of the 45 patients developed ventricular arrhythmias, with ventricular tackycardia occurring in 2 per cent. Patients with coronary artery disease and/or depressed left ventricular function developed twice the incidence of ventricular arrhythmias with isometric than with dynamic exercise Thus, isometric exercise testing is of more value than dynamic exercise testing in unmasking latent ventricular arrhythmias in patients with heart disease.

The circulatory response to dynamic exercise, exemplified by walking and running, has been well characterized both in normal subjects and in patients with various forms of heart disease. However, many activities during daily life primarily involve static or isometric exercise, for example, lifting, carrying, or pushing heavy objects. The physiological aspects of isometric exercise in normal subjects have been studied in detail by Lind, McNicol, and Donald (1966) and Freyschuss (1970), while other studies have been reported in patients with heart disease (Cohn *et al.*, 1973; Ewing *et al.*, 1973; Fisher *et al.*, 1973; Grossman *et al.*, 1973; Haissly *et al.*, 1974; Krayenbuehl *et al.*, 1972; Ludbrook, Karliner, and O'Rourke, 1974; Mullins and Blomqvist, 1973; Quinones *et al.*, 1974; Siegel *et al.*, 1972).

The principal circulatory effects of dynamic and isometric exercise are different. Dynamic exercise causes an increase in heart rate and cardiac output, with a small increase in mean arterial pressure and a significant fall in systemic vascular resistance. Isometric exercise in normal subjects produces an increase in heart rate and cardiac output and a large increase in both systolic and diastolic arterial pressures, with little or no change in systemic vascular resistance.

The use of isometric exercise as a stress test for evaluation of left ventricular function has recently been explored in this laboratory by Matthews *et al.* (1974), Mitchell and Wildenthal (1974), and by others (Helfant, de Villa, and Meister, 1971; Jacobs *et al.*, 1970; Kivowitz *et al.*, 1971). We were impressed by the frequent occurrence of arrhythmias during isometric exercise performed in the course of our haemodynamic studies. The present investigation was undertaken to compare the incidence of arrhythmias during and after isometric and dynamic exercise in patients with heart disease.

Patients and methods

Fifty-five patients were continuously monitored by electrocardiography during both isometric and dynamic exercise. The group included 35 men and 10 women, with a mean age of 54·5 years (range 28-78 years). Twenty-three patients had ischaemic heart disease, 18 had valvular heart disease, 3 had primary myocardial disease, and one patient had a residual post-traumatic right bundle-branch block. According to the New York Heart Association classification, 2 patients were in functional class I, 20 in class II, and 23 in class III. Thirty-one patients underwent cardiac catheterizations. No patient was on antiarrhythmic therapy at the time of study, and no patient had ectopic activity at rest during a 5-minute control period.

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A. Isometric exercise (handgrip)

Isometric exercise was performed using a spring-loaded handgrip dynamometer.[1] After determining the force of a maximal voluntary contraction by averaging the results of three different maximal efforts, the patients performed a sustained 25 per cent maximal voluntary contraction for 3 to 5 minutes, with an average duration of 4 minutes. After a 5-minute rest period, the patients performed a 50 per cent maximal voluntary contraction until fatigue set in; the average duration of the 50 per cent voluntary contraction was 1 minute, with a range of 30 seconds to 3 minutes. Care was taken to prevent a Valsalva manoeuvre. Of the 45 patients, 23 were examined by non-invasive techniques, and 22 patients were examined during cardiac catheterization.

The 23 patients examined by non-invasive techniques were monitored with continuous recording of the Frank lead electrocardiogram at a paper speed of 10 mm/s. Records at paper speeds of 25 or 50 mm/s were obtained during rest, the last minute of exercise, immediately after exercise, and 3 minutes after exercise. Indirect brachial artery pressure was recorded every 30 seconds during exercise and every minute during recovery with a semi-automatic device,[2] with the cuff placed on the resting arm.

Twenty-two patients were examined during cardiac catheterization with continuous and simultaneous recordings of the electrocardiogram, brachial artery pressure, and left ventricular pressure recorded on an Electronics for Medicine recorder at varying paper speeds of 10, 25, and 100 mm/s. Cardiac output was measured at rest and during the last minute of exercise at each load level by the indicator-dilution method. All cineangiograms were performed after completion of the exercise study. The ejection fraction was determined according to the method of Greene *et al.* (1967), from single plane (right anterior oblique) cineangiograms.

B. Dynamic or bicycle exercise

The 45 patients also performed dynamic exercise at progressive loads on a mechanically-braked bicycle ergometer. The duration of exercise at each load was 5 minutes, with a 5-minute rest period between work loads. Selection of the initial work load was based on the patient's history. Patients in functional class I and II began exercise at 300 kpm/min and patients in class III at 150 kpm/min or at no load except for the internal resistance of the ergometer. The load was increased in steps of 150 kpm/min. The test was carried to a symptom-limited maximal load unless the patient developed progressive horizontal ST depression of at least 0·1 mV (1 mm), or unless an increasing number of premature ventricular contractions, multifocal premature ventricular contractions, or runs of two or more occurred. The indications for discontinuing exercise conformed to the standards presented by Rochmis and Blackburn (1971). The technique for monitoring by electrocardiogram was identical to that used during the non-invasive isometric exercise test. Indirect arterial blood pressure was recorded during the last minute of exercise at each work load as with isometric exercise.

The bicycle test was performed on a separate day within one week of the handgrip test in 22 of the patients. The two tests were done on the same day in 23 patients. Isometric exercise always preceded dynamic exercise, with a rest period of at least one hour between the two tests.

C. Definition of arrhythmias

Any patient with an arrhythmia during rest or control periods was eliminated from the study. Ventricular tachycardia was defined as 3 or more successive premature ventricular contractions. A single premature contraction was counted as an arrhythmia.

Results

Mean data on work load, heart rate, and blood pressure during handgrip and bicycle exercise are presented in Table 1. The mean peak heart rate ± the standard error with isometric exercise was 86±2 beats/minute while it was 122±4 beats/minute with dynamic exercise. The mean peak systolic blood pressure was 179±6 mm Hg (23·8±0·8 kPa) with isometric exercise and 167±5 mmHg (22·2±0·7 kPa) with dynamic exercise.

The incidence of various arrhythmias is presented in Table 2 and Fig. 1. Arrhythmias were found more frequently in patients during the isometric exercise test than during the bicycle test, 44% (20 of 45) of patients compared to 24% (11 of 45) ($P < 0{\cdot}05$[3]). The number of patients having arrhythmias with handgrip at the 25 per cent maximal voluntary contraction level was 11 per cent (5 of 45).

Premature atrial contractions were equally common with both types of exercise and were seen in 11 per cent (5 of 45) of the patients during the handgrip test and in 9 per cent (4 of 45) during the bicycle test. The incidence of ventricular arrhythmias was higher during the handgrip test, 38 per cent (17 of 45) compared with 22 per cent (10 of 45), but the difference was not significant. When single premature ventricular contractions were disregarded, 31 per cent (14 of 45) of patients had 2 or more contractions during the handgrip test compared with 20 per cent (9 of 45) during the bicycle test. A striking difference was observed in the incidence of ventricular tachycardia, 15 per cent (7 of 45) during the handgrip test and 2 per cent (1 of 45) during the bicycle test ($P < 0{\cdot}05$) (Fig. 1). All patients who had ventricular arrhythmias during the bicycle test also developed premature ventricular contractions and ventricular tachycardia during the handgrip test. Examples of arrhythmias are

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[1] C. H. Stoelting Company, Chicago, Illinois.

[2] Narco Systems, Inc., Houston, Texas.

[3] χ^2.

TABLE 1 *Work load, heart rate, and arterial blood pressure at peak levels of handgrip and bicycle exercise*

	*Work load**	*Heart rate*	*Blood pressure (mmHg)* *Systolic*	*Blood pressure (mmHg)* *Diastolic*
Handgrip exercise	35±6	86±2	179±6	127±6
Bicycle exercise	391±31	122±4	167±5	94±3

*Work load expressed as kilopond-metres/minute for bicycle exercise and as force in kilograms for isometric exercise. Mean±SE, n=45.
Conversion from Traditional Units to SI Units: 1 mmHg≈0·133 kPa.

TABLE 2 *Incidence of arrhythmias with isometric exercise and dynamic exercise*

Diagnosis	*No. pts*	*Isometric exercise* *PAC's*	*Isometric exercise* *PVC's*	*Isometric exercise* *VT*	*Dynamic exercise* *PAC's*	*Dynamic exercise* *PVC's*	*Dynamic exercise* *VT*
Ischaemic heart disease	23	3	8	4	1	5	1
Valvular heart disease	18	0	6	1	2	3	0
Primary myocardial disease	3	2	2	1	1	2	0
Cardiac contusion	1	0	1	1	0	0	0
All diseases	45	5 (11%)	17 (38%)	7 (15%)	4 (9%)	10 (22%)	1 (2%)

Abbreviations: PAC, premature atrial contractions; PVC, premature ventricular contractions; VT, ventricular tachycardia.
Four patients had both PAC's and PVC's or VT. Patients with VT are included in the PVC column.

illustrated in Fig. 2, 3, and 4. A comparison of arrhythmias by cardiac diagnoses during isometric and dynamic exercise is illustrated in Fig. 5.

To exclude the possibility that catheter-induced arrhythmias affected our results, the incidence of arrhythmias during handgrip exercise in a group of patients with ischaemic heart disease who were catheterized was compared with a group of patients examined by non-invasive techniques. The patients were matched with respect to age and the severity of angina. Five of 10 (50%) patients studied during cardiac catheterization had arrhythmias compared with 30 per cent (4 of 13) in the group studied by indirect techniques. This difference was not significant between invasive and non-invasive techniques (P > 0·2). Four episodes of ventricular tachycardia were seen in the catheterized patients and 3 episodes were seen in the patients studied by non-invasive methods. All patients were excluded who, during catheterization, had arrhythmias at rest or during control periods with the catheters in place.

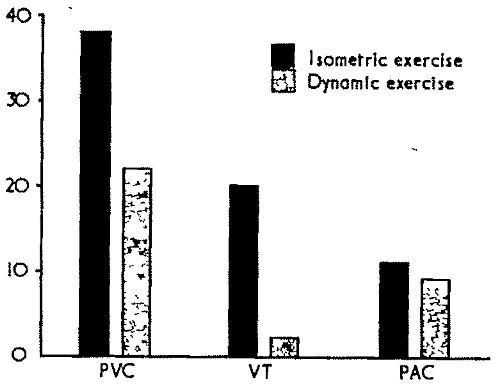

FIG. 1 *Incidence of arrhythmias induced by isometric and dynamic exercise stress testing in 45 patients. PVC, premature ventricular contraction; VT, ventricular tachycardia; PAC, premature atrial contraction.*

Twenty-one patients had left ventricular cineangiograms. Patients with ventricular arrhythmias had a mean ejection fraction of 46 per cent, suggesting that arrhythmias are more common with deteriorating left ventricular function.

Nine patients had ischaemic heart disease documented by coronary cineangiography. Ventricular arrhythmias occurred in 3 of 4 patients with triple-vessel disease, 1 of 3 patients with 2-vessel disease, and 1 of 2 patients with single-vessel disease, suggesting that arrhythmias were more common in patients with more severe coronary artery disease; however, the number of patients is too small for this trend to be significant.

Individual heart rate, blood pressure, and heart rate-systolic blood pressure product data in a subgroup of 11 patients with angina pectoris and ST

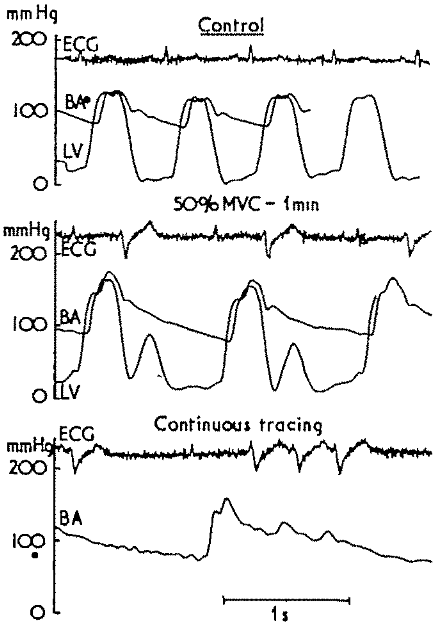

FIG. 2 *An example of ventricular arrhythmias occurring during isometric stress testing during cardiac catheterization. No arrhythmia was present before testing. The handgrip was released and the patient returned to normal sinus rhythm. BA, brachial artery pressure; LV, left ventricular pressure; MVC, maximal voluntary contraction; 50 per cent MVC 1 min, 50 per cent maximal voluntary handgrip contraction held for 1 minute.*

depressions during bicycle exercise are presented in Fig. 6. Mean maximal heart rate was 84 during handgrip exercise and 118 during bicycle exercise. Peak systolic blood pressure was slightly higher during handgrip, 188 mmHg (25·0 kPa), than during bicycle exercise, 175 mmHg (23·3 kPa). The heart rate-systolic blood pressure product/100 was higher during bicycle exercise, 207, compared with 158 with isometric exercise.

Discussion

Ventricular arrhythmias are frequently seen in patients undergoing exercise stress tests using dynamic exercise methods. We found that 22 per cent of the patients with heart disease in this study developed arrhythmias, a similar incidence to that of other reported series.

Kosowsky *et al.* (1971) reported 26 per cent ventricular arrhythmias during a treadmill test in patients who were free from arrhythmias at rest. Other investigators have reported ventricular arrhythmias in 10 to 39 per cent of cardiac patients undergoing treadmill or bicycle exercise tests, but quantitative comparison between series is difficult because of the differences with respect to patients, exercise test modes, monitoring techniques, diagnostic criteria, and antiarrhythmic therapy.

Ventricular arrhythmias are rare among young normal subjects during dynamic exercise but the incidence increases sharply with increasing age. Strandell (1963) found at least occasional premature ventricular contractions in 32 per cent of apparent

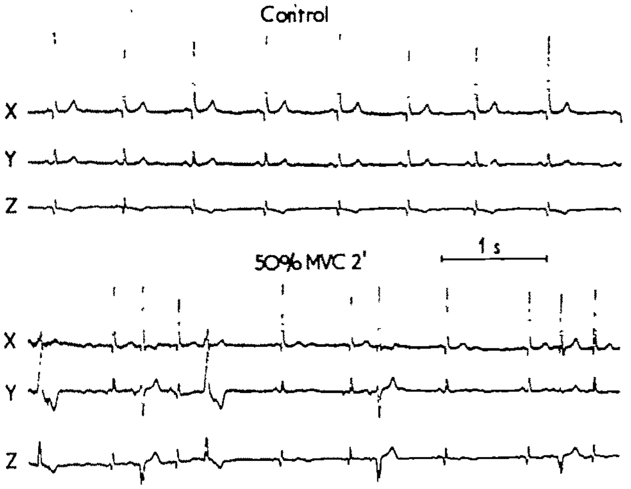

FIG. 3 *An example of arrhythmias developing during isometric stress testing using xyz Frank lead system. Multifocal ventricular as well as supraventricular arrhythmias are present. 50 per cent MVC 2', 50 per cent maximal voluntary handgrip contraction held for 2 minutes.*

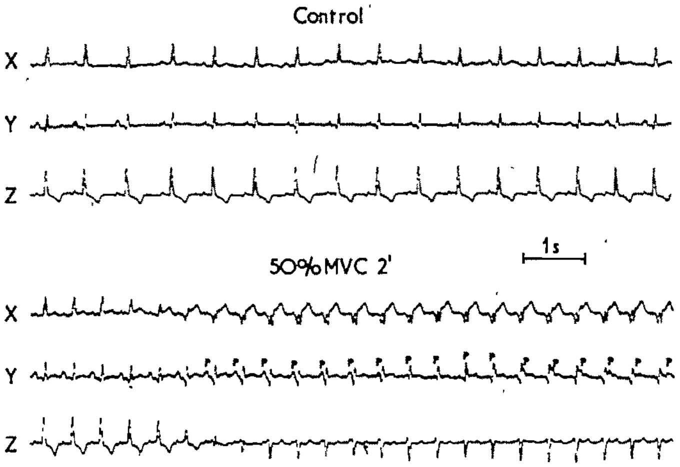

FIG. 4 *An example of ventricular tachycardia occurring during isometric stress testing. See Fig. 3 for abbreviations.*

healthy men, age 60 to 83, who performed maximal or near-maximal bicycle exercise. Ellestad *et al.* (1969) saw 9 cases of ventricular tachycardia among 1000 asymptomatic middle-aged subjects during or after a progressive treadmill test. Similar findings have also been reported by Gooch and McConnell (1970).

The surprising finding in this study was the high incidence of ventricular arrhythmias during isometric stress testing. Thirty-eight per cent of the

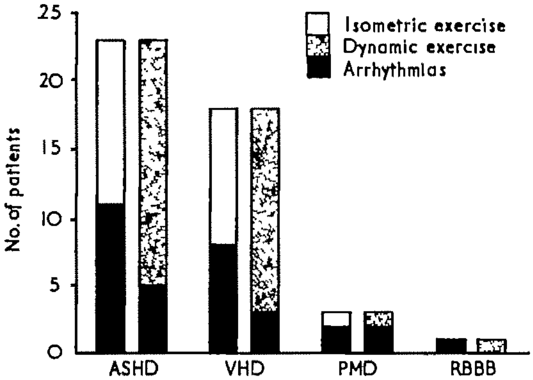

FIG. 5 *Comparison of arrhythmias by cardiac diagnoses during isometric and dynamic exercise. ASHD, ischaemic heart disease; VHD, valvular heart disease; PMD, primary myocardial disease; RBBB, right bundle-branch block caused by a cardiac contusion.*

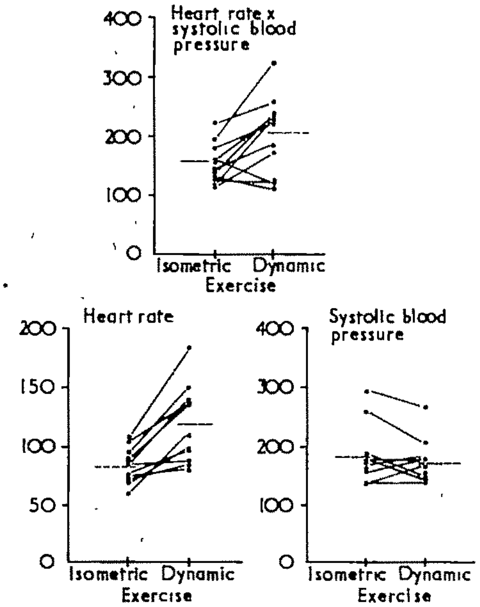

FIG. 6 *Heart rates and systolic blood pressures in 11 patients with angina pectoris during isometric and dynamic exercise. The solid lines connecting dots represent individual patients. The dashed lines are the group means. In the upper panel are plotted the maximal heart rate × systolic blood pressure/100 during both isometric and dynamic exercise. In the lower left-hand panel are plotted the maximal heart rates during both isometric and dynamic exercise.*

patients developed ventricular arrhythmias, a 16 per cent increase above the incidence with dynamic testing. Arrhythmias with isometric exercise in normal subjects are unusual. We have seen only a single premature ventricular contraction in 2 of 60 normal subjects during isometric stress testing. Other reports (Cohn *et al.*, 1973; Fisher *et al.*, 1973; Grossman *et al.*, 1973; Haissly *et al.*, 1974; Helfant *et al.*, 1971; Kivowitz *et al.*, 1971; Krayenbuehl *et al.*, 1972; Ludbrook *et al.*, 1974; Matthews *et al.*, 1974; Mitchell and Wildenthal, 1974; Mullins and Blomqvist, 1973; Prakash *et al.*, 1972; Quinones *et al.*, 1974; Siegal *et al.*, 1972) have indicated only occasional arrhythmias; however, these studies were not designed to look specifically for arrhythmias, and continuous electrocardiographic recordings were not always made. Furthermore, no comments were made regarding the use of antiarrhythmic therapy before exercise testing.

In this series all patients who developed arrhythmias did so at 50 per cent maximal voluntary contraction, a higher isometric stress than used by other investigators. The incidence of ventricular arrhythmias was only 11 per cent in this series at 25 per cent maximal voluntary contraction.

The incidence of ventricular arrhythmias and especially ventricular tachycardia was high in patients with ischaemic heart disease and in those with abnormal ventricular function. Those patients with depressed ejection fraction and those with severe coronary disease on coronary angiography had a 50 per cent incidence of ventricular arrhythmias during isometric stress testing.

The reasons for the high incidence of ventricular arrhythmias during isometric exercise in patients with heart disease is not clear. A more intense sympathetic drive during isometric than during dynamic exercise is a possible but unlikely explanation. Physiological studies by Lind *et al.* (1966) and by Freyschuss (1970) suggest that the heart rate increase during isometric exercise is primarily mediated by vagal withdrawal. The rate acceleration during dynamic exercise at low work load levels is also primarily the result of vagal withdrawal, but sympathetic stimulation becomes increasingly important at higher loads (Robinson *et al.*, 1966). The arrhythmia-suppressing effect of an increased heart rate is well known, i.e. sinus tachycardia overdrive of the ventricular arrhythmia. The occurrence of chest pain and ischaemic ST depressions more frequently during dynamic exercise in the patients with ischaemic heart disease and the peak heart rates and heart rate-systolic blood pressure products during exercise indicate that peak myocardial oxygen demand was higher during dynamic exercise. The higher incidence of ventricular arrhythmias during isometric exercise when compared with dynamic exercise may be related to a lower heart rate at any given level of cardiac work (Fig. 6).

The high incidence of serious ventricular arrhythmias with isometric stress testing in this study suggests that stress tests based on isometric exercise should be performed where facilities for monitoring and resuscitation are available. It also seems prudent to discourage activities requiring heavy isometric exercise in patients with heart disease because of the chance of sudden death induced by ventricular tachycardia or fibrillation.

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'Isolated' pulmonary valve stenosis as part of more widespread cardiovascular disease

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In 25 patients aged 6 days to 9 years presenting as 'isolated' pulmonary valve stenosis, histology of the myocardium of right and left ventricles, coronary arteries, and ascending aorta has shown abnormality in one or all these areas. Myocardial necrosis, old and recent, unrelated to coronary occlusion was frequent. Myocardial 'dysplasia' involving both ventricles, and resembling hypertrophic cardiomyopathy (HOCM, ASH) was found in 10 and a relation of this to myocardial injury in the fetus is postulated. Varying degrees of coronary occlusion were frequently seen in both right and left coronary arteries. The histology of the ascending aorta was abnormal showing 'higgledy-piggledy' disorder of smooth muscle components in 12 (48%).

In a different series of 53 patients who had pulmonary valvotomy for apparent 'isolated' pulmonary valve stenosis there were 14 with clinical evidence of left ventricular abnormality consistent with the pathological changes described, 2 with the same aortic histological changes, and 2 with macroscopical left ventricular hypertrophy. Two of them developed classical hypertrophic cardiomyopathy years later.

It is suggested that when pulmonary valve stenosis presents with a thick tricuspid poorly mobile valve, particularly in infants or in patients with evidence of other congenital stigmata, it may be part of a more widespread cardiovascular abnormality. This should be recognized and considered in the evaluation of surgical patients and late survivors who may show unexpected clinical features.

Isolated pulmonary valve stenosis with intact ventricular septum is an example of a simple congenital obstruction to blood flow. It has been assumed that surgical opening of the narrow pulmonary valve solves the patient's problem. This straightforward concept has remained unchallenged over the years.

Responsibility for this restricted view may lie on the shoulders of the pathologists. What appeared to be a consistently dome-shaped valvar obstruction with predictable functional muscular hypertrophy proximal to it has not stimulated further research into the true nature and extent of the disease. Specimens have been described routinely with perfunctory mention of the diameter of the valve orifice, the number of cusps, and the thickness of the right ventricular wall and then, more often than not, destroyed.

The purpose of this paper is to report a new aspect of the disease hitherto described as simple pulmonary valve stenosis. Fresh evidence suggests that in some patients the fusion of the pulmonary valve cusps should be looked upon as the end result of a disease of the fetus which is not necessarily limited to the pulmonary valve, since striking changes may also be present in myocardial architecture in one or both ventricles, in the coronary arteries, and in the aortic wall. Before valvotomy, the dominant manifestations of right ventricular outflow obstruction may obscure the functional significance of these other pathological changes. After apparently successful surgical relief of the obstruction, one or some of the other features of the underlying disease may become obvious though this does not happen in every patient.

Long-term follow-up of survivors after pulmonary valvotomy and retrospective scrutiny of the postoperative course of patients under 3 years of age with severe pulmonary stenosis have revealed some unexpected clinical features which also suggest that the disease may not be limited to the pulmonary valve in every patient.

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Subjects and methods

Twenty-five specimens preserved in formalin from patients with 'isolated' pulmonary valve stenosis were available for study in the pathology department of the Children's Hospital, Buenos Aires. The ages ranged from 6 days to 9 years—9 were over 1 year. Cases of pulmonary valve stenosis in young infants with a small tricuspid ring diameter were excluded arbitrarily since the clinical picture is different and it is apparent that in them the disease is not confined to the pulmonary valve. By definition none had associated ventricular septal defects or other obvious structural congenital cardiovascular abnormalities. A patent foramen ovale, flaccid or distended, was the rule, and none had a true atrial septal defect; one patient had a closed intact atrial septum.

Eighteen patients with clinical evidence of severe pulmonary stenosis had been operated upon and died hours to 6 days after operation. The other 7 patients died before operation, a few hours or days after admission for undetermined causes, and after cardiac catheterization in one instance. There were no stigmata of rubella outside the cardiovascular system such as cataracts, hepatitis, or diffuse purpura, but rubella as the aetiology cannot be excluded in some because of incomplete clinical data.

Seven to 15 random blocks were taken from the myocardium of both ventricles. Further blocks of tissue were taken containing the main coronary arteries and a sizeable portion of the adjacent muscle, and transverse tissue blocks with the ascending trunk of both the aorta and the pulmonary artery in one section. Paraffin-embedded sections were stained routinely with P.A.S.-haematoxylin, Gomori's aldehyde fuchsin stain for elastic tissue and Masson's trichrome stain for muscle and connective tissue. In selected cases, stains for calcium were used, and also the tetrazolium technique to show necrotic muscle. All slides were evaluated by 2 observers unaware of the clinical details.

Smooth muscle changes in the coronary arteries were graded into 3 categories (Table 1). They were considered to be of 'moderate' severity when more than half the random sections showed normal arteries and the others had the segmental musculo-elastic dysplasia described by Neufeld (1974). Cases were classified as having 'widespread' coronary pathology when these moderate changes were present in all random sections, yet only rarely encroaching seriously upon the lumen. 'Severe' coronary obstructive lesions were those that reduced the lumen of subepicardial arteries by 75 per cent or more; cases were included in this category if this degree of obstruction was present in one or more sections irrespective of what was found in other areas.

TABLE 1 *Summary of pathological changes in 25 patients with 'isolated' pulmonary valve stenosis*

Right ventricular pathology			
(a) *Coronary arteries*	Obstructive	moderate	6
		widespread	10
		severe	7
	Unusually dilated		2
(b) *Myocardium*		necrosis	12
		'dysplasia'	10
		normal	3
Left ventricular pathology			
(a) *Coronary arteries*	Obstructive	widespread	7
		severe	3
		normal	15
(b) *Myocardium*		necrosis	3
		'dysplasia'	7
		normal	15
Aortic wall pathology			
		abnormal	12
		normal	13

Areas of myocardial cell death (necrosis) were considered to be significant when more than one-half of a mid-power (×40) microscopical field was involved. 'Recent' myocardial cell necrosis was diagnosed when the obvious nuclear and cytoplasmic changes were associated with a minimal or no inflammatory reaction. 'Healed myocardial necrosis' was recognized as an area of replacement fibrosis, usually quite dense and uniform but rarely extending beyond a low-power (×10) microscopical field.

Results

Histopathological study

Eighteen of the pulmonary valves had been opened at surgery so that verification of the residual diameter of the stenotic orifice was inexact. Three were noted to have an eccentric orifice on the original surgical protocol. In 19 specimens the valves were thickened by oedematous stiff connective tissue and it was difficult to distinguish the line of fusion between cusps, but in all there was a clear raphe at the attachment of the valvar tissue to the pulmonary wall indicating the past existence of a tricuspid primordia in every specimen (Fig. 1). There was no example of a stenosed bicuspid pulmonary valve. In the other 6 patients the valvar tissue was thinner, pliable, and tricuspid, almost transluscent. Four of these were aged 2, 4, 7, and 9

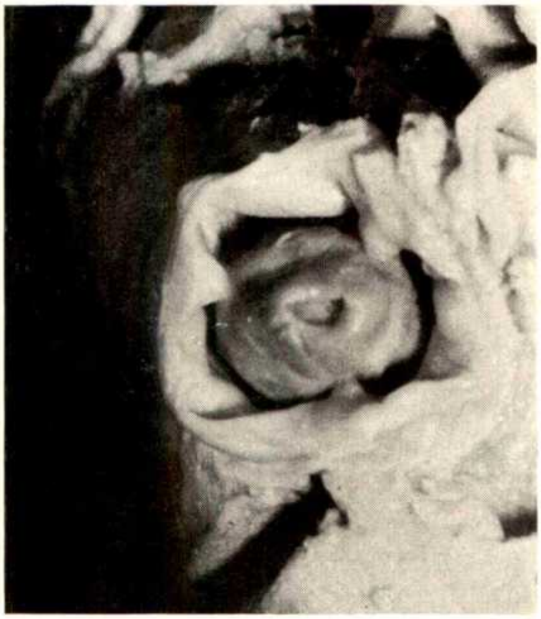

FIG. 1 *Typical thickened tricuspid pulmonary valve stenosis from child aged 4 months who died before surgery. Child had extensive areas of myocardial necrosis in both ventricles and occlusive coronary artery changes of moderate severity in the right ventricle.*

years and the other 2 were less than 1 year of age.

The histological findings are summarized in Table 1. The coronary arteries in the right ventricle were abnormal in every patient. The changes were considered to be of moderate degree in 6 and were widespread in a further 10. Seven patients had severely obstructive lesions (Fig. 2) and all of them were less than 6 months of age. In 2 patients, aged 6 and 8 months, the main and also the intramyocardial arteries were unusually dilated, almost double the normal diameter, but neither showed abnormality of the muscular media or the intima. In both, the histology of the ascending aorta was abnormal showing the typical 'higgledy-piggledy' disorder to be discussed later.

The left ventricular coronary arteries showed no significant abnormality in 15 patients and widespread changes in the subepicardial coronary arteries in 7, all of whom had similar lesions in their right coronary arteries. Severe obstructive lesions were found in coronary arteries on the right in 7 and were also present on the left in 3 of this group.

Histological evidence of recent and/or healed myocardial necrosis was found in the right ventricular wall of 12 patients, in 3 of whom it was also present in the left ventricular wall. As is characteristic in infants, necrotic areas were frequently small and spotty, sometimes coalescing to account for 50 per cent of a low-power field. In addition to the usual discrete inflammatory and macrophage reaction around areas of relatively recent necrosis, mitosis in myofibres was noted in patients under 6 months of age and occasionally pigment deposition was a prominent feature. Since random sections were used, no attempt could be made to quantify the total amount of necrosed myocardium which in 4 specimens was impressive. Even though dating of reparative stages in infancy is imprecise, it was considered that in all these 12 patients myocardial cell necrosis had occurred, at least in part, before operation. In 4 of the 7 patients dying before operation, recent necrosis was a prominent feature. Healed myocardial necrosis was seen as scattered areas of fibrosis, sometimes quite extensive and localized and often interspersed with strands of viable muscle. Characteristically these scars did not follow coronary artery distribution patterns and were not preferentially subendocardial. In 2 of these patients some areas of scarring were associated with the appearances of 'nodular' proliferation of muscle giving rise to a picture curiously similar to some forms of post-necrotic hepatic cirrhosis.

In 10 patients extensive areas of morphological disarray and malalignment of myofibres (Fig. 3) referred to in this paper as myocardial 'dysplasia' were found in sections from the right ventricle. In 7 this change was present in the left ventricle: 4 of these showed the same appearances in sections from right ventricular myocardium. In these areas of 'dysplasia', muscle bundles and single fibres coursed in different directions in a disorderly fashion, forming occasional whorls often at right angles to one another (Fig. 3a and b). The extent and distribution of areas of myocardial 'dysplasia' could not be fully assessed because of the random sampling of ventricular tissue, but it was present in both ventricular septum and the muscle of the free wall and on occasions could be seen by the naked eye (Fig. 3c). None showed localized asymmetrical septal hypertrophy.

Histological examination of the wall of the macroscopically normal ascending aorta showed a disarray and malalignment of its smooth muscle components in 12 patients (Fig. 4), 2 of whom had widely dilated coronary arteries, 3 had moderate coronary changes, 2 were severe, and 5 were widespread. The aortic changes were most obvious with elastic tissue stains since the elastic laminae follow the spatial distribution of the smooth muscle cytoplasm (Fig. 4). Typically the elastic fibres were

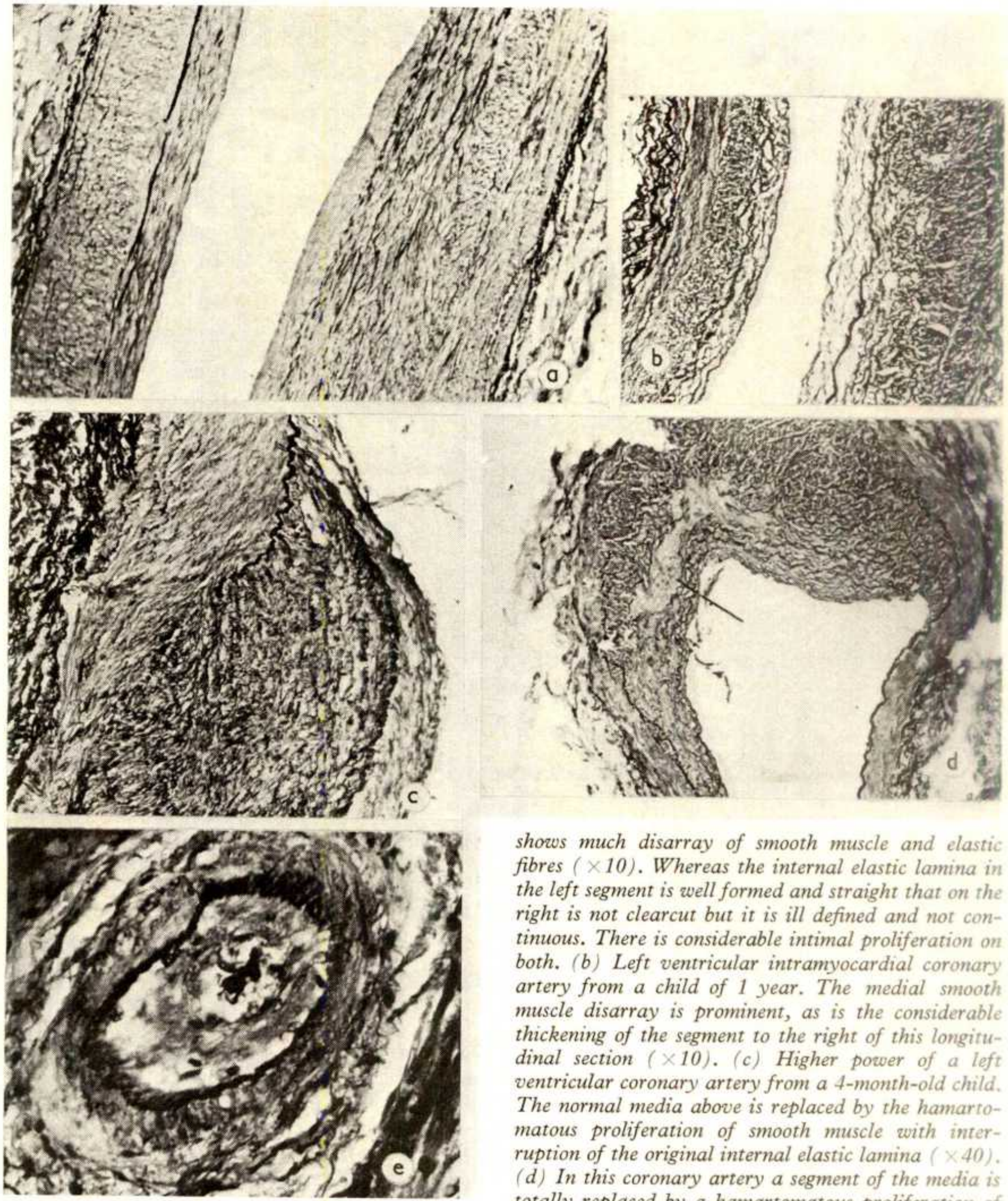

FIG. 2 *Coronary arterial pathology in 'isolated' pulmonary valve stenosis. Sections stained with Gomori's aldehyde fuchsin stain for elastic tissue. (a) Longitudinal section of a right ventricular coronary artery from 6-day-old baby. The media to the right is twice as thick as the opposite wall and shows much disarray of smooth muscle and elastic fibres (×10). Whereas the internal elastic lamina in the left segment is well formed and straight that on the right is not clearcut but it is ill defined and not continuous. There is considerable intimal proliferation on both. (b) Left ventricular intramyocardial coronary artery from a child of 1 year. The medial smooth muscle disarray is prominent, as is the considerable thickening of the segment to the right of this longitudinal section (×10). (c) Higher power of a left ventricular coronary artery from a 4-month-old child. The normal media above is replaced by the hamartomatous proliferation of smooth muscle with interruption of the original internal elastic lamina (×40). (d) In this coronary artery a segment of the media is totally replaced by a hamartomatous proliferation of smooth muscle, with disappearance of the internal elastic lamina. The arrow indicates an early accumulation of foamy myocytes. The patient was 8 days of age (×10). (e) An intramyocardial artery in the left ventricle of a 2-month-old patient showing almost total occlusion (×40).*

short, stumpy, and not parallel to each other, referred to as 'higgledy-piggledy' arteriopathy (Beçu and Gallo, 1974), which by definition is 'without any order of position or direction, in jumbled confusion' (*Shorter Oxford English Dictionary*, 1944). Eleven patients with aortic changes had thickened lumpy pulmonary valves (Fig. 1) and in one the cusps were thin and more pliable. Myocardial dysplasia was present in 7 with aortic changes, and evidence of myocardial necrosis, old and recent, was equally distributed between those with or without aortic changes. In this series other systemic arteries were not available for study. Evaluation of elastic and muscular changes in the pulmonary artery was difficult because of the uncertainty created by the normal involution of its initial aorta-like wall pattern enhanced by poststenotic dilatation.

Possible clinical correlations

In an attempt to see if there were clinical features which correlated with the above pathological findings, the postoperative course was studied in a different series of 53 patients who had open pulmonary valvotomy for apparently 'isolated' pulmonary valve stenosis. Patients with tricuspid valve abnormalities, true atrial septal defect, and any other obvious structural abnormality in the heart were excluded.

The findings on the 10 youngest patients aged 7 to 30 months, with preoperative right ventricular pressures 95 to 250 mmHg (12·6 to 33·3 kPa), are summarized in Table 2. Whether left ventricular disease can account for the low output state and death in 3 is uncertain; one patient at necropsy had a large left ventricle (Fig. 5), but there is no histological information available in any nor are the other 2 specimens available to us for inspection. Presumably left ventricular disease was present in the

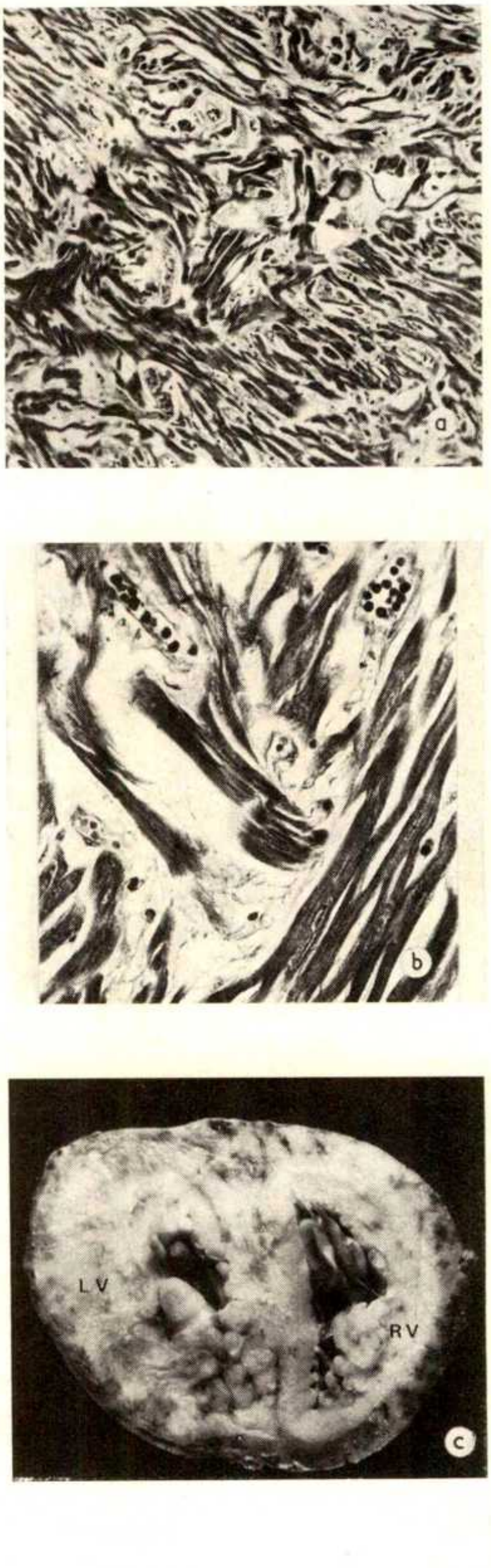

FIG. 3 *Myocardial 'dysplasia' in patients with 'isolated' pulmonary valve stenosis. (a) ×8 (b) ×31. Section from the left ventricle of a child aged 2 years stained with Masson's trichrome. This illustrates the characteristic and striking malalignment and disarray of myocardial fibres, coursing in all directions and even at right angles to each other. (c) Transverse view of both ventricles of child aged 14 months who died after pulmonary valvotomy. The left ventricle (LV) free wall is appreciably thicker than the right ventricle (RV).* →

3 who survived, having had dyspnoea and radiological evidence of pulmonary oedema in the early postoperative days, since no structural lesion has been found to account for this course. One child 7 years later has developed electrocardiographic left ventricular hypertrophy, judged from voltage changes, and the other 2 children appear to be normal but have not been fully investigated. One boy had the stigmata of Noonan's syndrome (Noonan and Ehmke, 1963).

In an older group of 43 patients aged 3 to 20 years with right ventricular pressures 75 to 190 mmHg (10·0 to 25·3 kPa), there were 8 with obvious features suggesting left-sided cardiovascular involvement (Table 3). The child in whom an aortic biopsy showed 'higgledy-piggledy' arteriopathy (Fig.

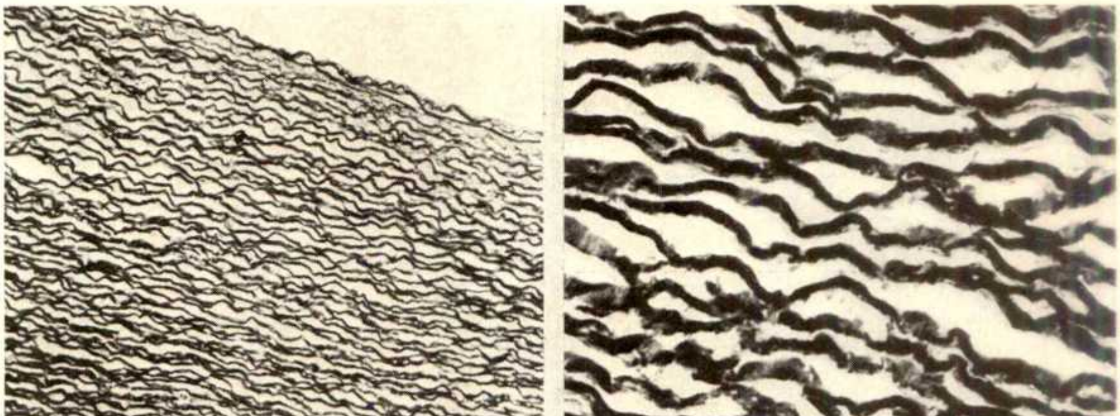

FIG. 4 *Sections from the normal ascending aorta of a 5-month-old child who died from gastro-intestinal disease in comparison with the aorta from a 6-month-old child who died with severe pulmonary valve stenosis. (a) (×9) and (b) (×35) from the normal child showing ordered parallel elastic fibres. (c) (×9) and (d) (×35) from the baby with pulmonary valve stenosis showing disorganization of elastic fibres with breaking up of elastic laminae which follow the smooth muscle components, typical appearances given the name 'higgledy-piggledy' disorder. Sections stained by Gomori's stain for elastic tissue.*

6) had rubella syndrome which was not present in the other patients. At the time of pulmonary valvotomy 5 years earlier, the pulmonary artery pressure was 45/22 mmHg (6·0/2·9 kPa) despite a gradient of 160 mmHg (21·3 kPa) across the narrow pulmonary valve. He then developed severe left ventricular hypertrophy and was operated on for what was found to be mild tricuspid aortic valve stenosis

TABLE 2 *Postoperative findings suggesting diffuse cardiovascular involvement in 10 children aged 7 to 30 months who had pulmonary valvotomy*

Low cardiac output state	6	3 dead, 1 PM large left ventricle*
		3 pulmonary oedema (x-ray)
		↓
		1 LVH (electrocardiogram) 2 'normal'
Systemic systolic hypertension BP 140 to 160/100 mmHg (18·6 to 21·3/13·3 kPa)	2	

*No histology available.

PM=post mortem.

LVH=Left ventricular hypertrophy.

TABLE 3 *Operative and postoperative clinical findings suggesting more diffuse cardiovascular abnormality in 8 of 43 patients aged 3 to 20 years at pulmonary valvotomy*

Pulmonary oedema	3	1 dead (PM large left ventricle)
		1 developed HOCM 6 years later
		1 abnormal left ventricle on angiography 8 years later
At operation large left ventricle, small aorta	2	1 dead* PM
		1 LVH (electrocardiogram)
Systemic systolic hypertension 140 to 175/90 to 100 mmHg (18·6 to 23·3/12·0 to 13·3 kPa)	2	
Biopsy of small aorta 'higgledy-piggledy'	1	
	8	

*In our opinion preliminary histology of small aorta showed classical 'higgledy-piggledy' and left ventricle was large. No further histology available.

PM=Post mortem.

HOCM=Hypertrophic obstructive cardiomyopathy proven at operation.

LVH=Left ventricular hypertrophy.

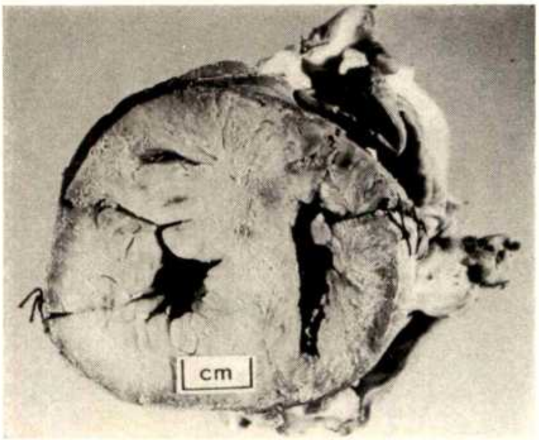

FIG. 5 *Transverse section through the heart looked at from above, from an 11-month-old child reported in the clinical series (Table 2) who died 2 days after pulmonary valvotomy having been in a persistent low cardiac output state. The left ventricle marked with a cm marker is obviously abnormally thickened as is the right ventricle. Streaks of fibrous tissue were evident on naked eye inspection.*

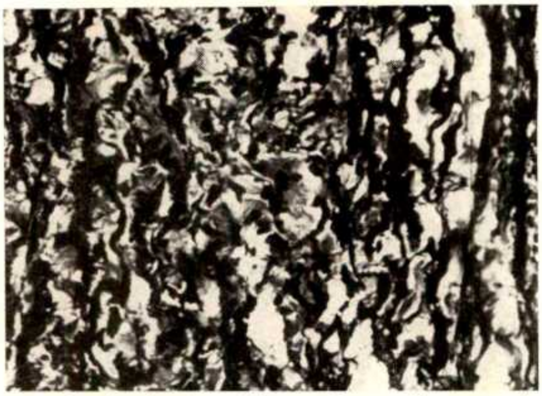

FIG. 6 *Section from biopsy of ascending aorta in boy aged 10 years with rubella syndrome who had severe pulmonary valve stenosis. There are 'higgledy-piggledy' changes with typical malalignment of elastic elements—stained with Gomori's aldehyde fuchsin (×25).*

associated with severe diffuse subvalvar hypertrophy. Two of the other 7 patients with unusual left-sided problems after valvotomy had raised pulmonary artery pressures 30 to 35 mmHg (4·0 to 4·7 kPa) before operation and none of the 7 had any structural disorder to account for the postoperative course. All these 8 patients had the thick tricuspid pulmonary valve stenosis already described, which was readily recognizable on right ventricular angiocardiography (Fig. 7).

In 1 of 3 patients, who developed postoperative dyspnoea and pulmonary oedema with left and right pleural effusions, the condition persisted for 2 months (Fig. 8). Investigation of this girl 8 years

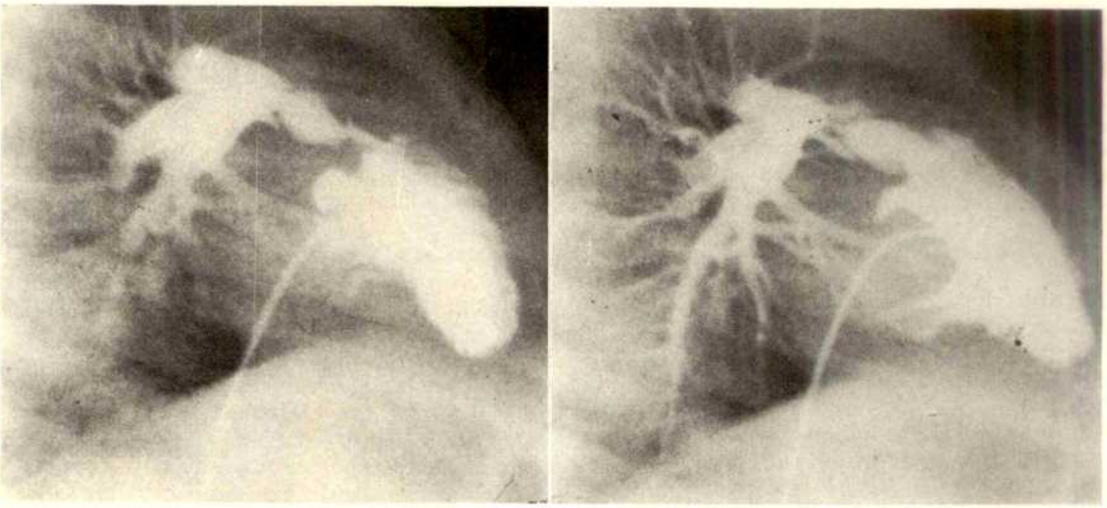

FIG. 7 *Right ventricular angiocardiograms (lateral view) from a 26-month-old child with the thick tricuspid lumpy valve. Though domed in systole, the cusps are obviously thick and make up an irregular thickened filling defect in diastole (b). This is the type of pulmonary valve stenosis found in all those with clinical evidence of more diffuse cardiovascular involvement.*

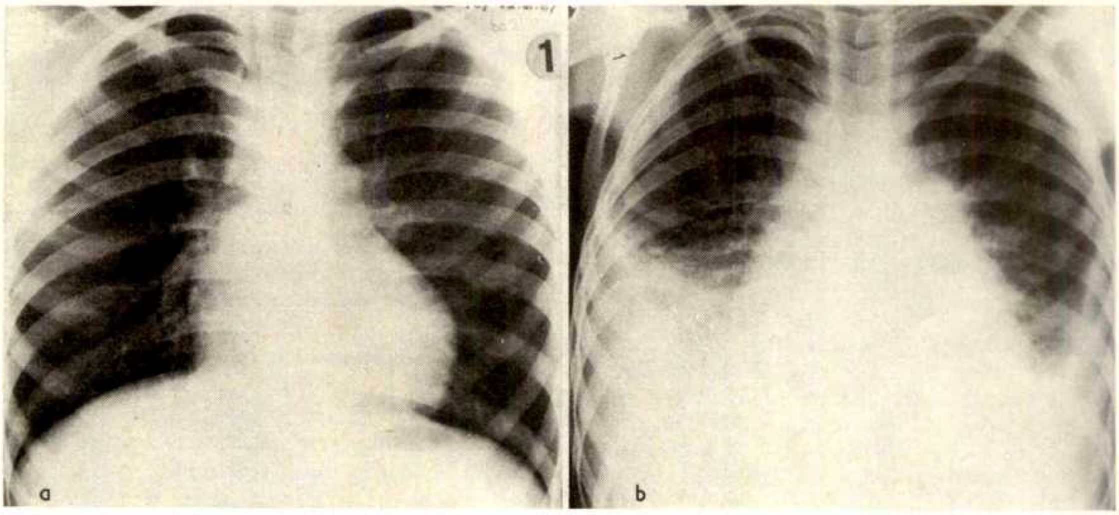

FIG. 8 *Chest* x-*ray films from a girl aged 11 years with severe pulmonary valve stenosis and resting right ventricular pressure of 180 mmHg (23·9 kPa): (a) before operation, (b) three weeks after operation, showing bilateral pleural effusions and pulmonary oedema which continued for 10 weeks.*

later showed abnormal thickening of the left ventricle with an A wave of 17 mmHg (2·3 kPa). The other child who survived a difficult postoperative period developed clinical features of obstructive cardiomyopathy which was confirmed by catheterization and resection of subaortic muscle 6 years after the pulmonary valvotomy.

Three of the 8 patients had Noonan's syndrome and the other 5 were somatically normal.

Incomplete survey of the other 35 patients has shown 3 patients with electrocardiographic signs of left ventricular hypertrophy and a further 5 have raised systemic blood pressure. These patients had the characteristic thick tricuspid valve but left ventricular function has not been investigated yet.

Discussion

Unexpected pathological abnormalities were found in the coronary arteries, in the myocardium of the right and left ventricles, and in the ascending aorta in a group of 25 patients who presented clinically as 'isolated' pulmonary valve stenosis. The finding of such widespread and serious pathological abnormality suggests that there has been generalized cardiovascular injury to the fetus even though the clinical signs relate only to the severe pulmonary valve stenosis.

Since widespread or severe coronary pathology was found in 17 of 25 specimens with 'isolated' pulmonary valve stenosis, and 12 of them had evidence of myocardial necrosis and focal fibrosis, a possible relation to each other must be considered. Myocardial necrosis in infancy can result from coronary occlusion as in adults (Gault and Usher, 1960) but it is unlikely to be a direct cause and effect in these patients because the severity of the myocardial changes, both old and recent, was unrelated to the severity of the coronary obstructive lesions, and the distribution of the myocardial fibrosis and necrosis did not follow the patterns of arterial supply. The same myocardial pathology was found by Franciosi and Blanc (1968) in different congenital heart malformations, including pulmonary valve stenosis, also in the absence of occlusive coronary artery abnormalities.

Prediction of the exact age and cause of myocardial necrosis seen microscopically in the infant heart is difficult. A fibrous replacement was obvious in some infants aged 1 and 17 days, so the acute necrosis must have occurred during intrauterine life, as has been previously documented (Clapp and Naeye, 1961).

Areas of recent necrosis were also found in older infants, some of whom had not had operation, suggesting that some new myocardial necrosis had occurred after birth. Berry (1967) reported similar myocardial damage in infants dying from a variety of conditions associated with anaemia, hypoxia, and hypotension. Thus, myocardial cell death may result in infants and children from disturbed cellular metabolism from several causes, just as Harris (1975) has postulated in adult myocardial infarction. Whatever the cause of the fetal injury or the pathogenesis of the cell death after birth, it appears to be common in severe isolated pulmonary valve stenosis and should be considered in clinical management.

The signs and symptoms of myocardial necrosis in infants with pulmonary stenosis may not be recognized within the general features of cardiac failure. Transient electrocardiographic changes may not be evident or may be missed and should not be expected to follow patterns characteristic of myocardial infarction in adults. Possibly some of the diffuse T wave changes so frequently seen in sick infants with various types of congenital heart disease are the result of myocardial necrosis and should not be so readily attributed to digitalis or dismissed as non-specific. Fresh necrosis may account for lethal arrhythmias and sudden death after catheterization and also the bad prognosis of severe pulmonary stenosis in infants after surgery. Persistent abnormal ventricular function after good surgical relief of obstruction may possibly be the result of old healed necrosis in both ventricles. Studies on the left ventricle after pulmonary valvotomy in the clinical series are inadequate to elucidate the frequency of left ventricular abnormality except in those where it was clinically obvious.

The extent of permanent damage to the myocardium by such early cell death is an interesting problem. The collateral circulation in the infant is plentiful, and myofibres retain part of the fetal capacity for reparative replication. The mitoses in cells around the dead area so frequently seen in this pathological series and reported by others (MacMahon, 1937; Esterly and Oppenheimer, 1966) support this contention. Long-term personal observation of 3 patients who survived myocardial infarction during infancy, in association with anomalous origin of the left coronary artery from the pulmonary artery, has shown that there is considerable anatomical, clinical, and electrocardiographic evidence of hypertrophy, which was pronounced in one patient operated on 13 years later (Somerville and Ross, 1970).

Although pathological observations in the clinical series are scant and in the few who died there was no histological material available, there were at least

2 in whom the left ventricle was large and fibrotic at necropsy, in addition to the clinical features summarized in Tables 2 and 3. In our opinion, preliminary histological investigation of the ascending aorta showed 'higgledy-piggledy' arteriopathy in the patient whose left ventricle was noted to be large at surgery, but further histological material was not available to us. Retrospective review of the opacified left ventricle seen on the late films from the right ventricular injection showed the left ventricle to be large and to contract abnormally and the small ascending aorta did not show the usual changes in size with diastole and systole. It may be that this left ventricular hypertrophy as also observed by Harinck (1974) in some late survivors with pulmonary stenosis may be a reactive development to earlier necrosis. Similarly dyspnoea, pulmonary oedema, and pulmonary effusion appearing after operation both in infants and occasionally in older patients may be secondary to this left ventricular disease.

Perhaps the most intriguing pathological finding in the myocardium is the appearance of disarray and malalignment of myocardial fibres referred to as 'myocardial dysplasia'. This may be another form of healing after fetal myocardial cell death or injury. It is likely that the myocardium, like other body tissues such as skin, has only a few limited ways of healing and this is one of them that can occur in the fetus or infant. On morphological grounds these appearances bear a resemblance to hypertrophic cardiomyopathy or asymmetrical septal hypertrophy (HOCM or ASH) (Ferrans, Morrow, and Roberts, 1972; Henry, Clark, and Epstein, 1973; Alexander and Gobel, 1974). The pathological evidence indicates that 'dysplasia' may involve extensive areas of both ventricles in some patients with pulmonary valve stenosis. Whether these patients would have developed later the classical clinical features of hypertrophic cardiomyopathy or just simple ventricular hypertrophy is unknown. Whether congenitally dysplastic myocardial fibres contract in an abnormal fashion and lead to further hypertrophy with necrosis and more fibrosis to give rise to the more classical histological features of hypertrophic cardiomyopathy or asymmetrical septal hypertrophy is also speculative. It may be relevant that the same sort of thick lumpy tricuspid pulmonary valve stenosis is the type found in Noonan's syndrome (Rainer-Pope *et al.*, 1964) as also in hypertrophic cardiomyopathy (Ehlers *et al.*, 1972) without added structural congenital heart disease. Furthermore, the frequent finding of an unusual electrical axis, either left anterior hemiblock or an unexpected deep S in lead II of the electrocardiogram in Noonan type patients presenting with 'lone, pulmonary valve stenosis, may also be related to the presence of septal or left ventricular muscle disease or fibrosis.

In these patients, as in other congenital syndromes associated with pulmonary valve stenosis, there is evidence because of the presence of the other extracardiac manifestations that the congenital disease is not confined to the pulmonary valve.

It is also considered that the microscopical abnormality of disordered muscular and elastic fibres referred to as 'higgledy-piggledy' arteriopathy in the aorta should be regarded as a healing response to fetal injury and has been found in other examples of probable fetal damage. For instance, it was pronounced in a group of children presenting with systemic hypertension and found at necropsy to have increased heart weights for no apparent structural cause (Beçu and Gallo, 1974), in familial arteriopathy (McDonald, Gerlis, and Somerville, 1969), in supra-aortic stenosis of various cases (Somerville and Beçu, 1976), and was also obvious in the ascending aorta of the child in the clinical series with rubella syndrome. With the exception of the family whose great arteries looked like 'macaroni', the aorta looked macroscopically normal in all the patients, and the 'higgledy-piggledy' nature of elastic and muscle fibres was a histological finding. Such a disorder of major conducting arteries must induce impedance to pulse wave transmission, and perhaps this may be the cause of the raised systolic blood pressure noted in some survivors of pulmonary valvotomy as well as those known congenital syndromes with aortopathy and arteriopathy already referred to.

From these pathological findings it is suggested that a noxious fetal injury may be caused by one of several factors: rubella, chemical, metabolic, or genetic factors, and thus lead to myocardial necrosis and aortic pathology and in some instances may cause pulmonary valve stenosis. If the fetus survives, the myocardium may heal with fibrosis and compensatory hypertrophy or peculiar 'dysplasia' which might progress to the clinical picture of hypertrophic cardiomyopathy with or without 'higgledy-piggledy' aortopathy, another manifestation of healed disorder smooth muscular elements in the cardiovascular system.

Such theories if true may explain some of the associations of hypertrophic obstructive cardiomyopathy with other congenital heart abnormalities (Somerville and McDonald, 1968), and with strange congenital syndromes involving other organs outside the cardiovascular system, with or without pulmonary valve stenosis. All the clinical group with obvious evidence of left ventricular abnormality had the thick tricuspid pulmonary valves, as described in the pathological series. However, serious myocardial and aortic changes were seen also in 4 of the 6 patients with thin tricuspid pulmonary valves. The pathological data are not extensive enough to show a significant difference between those with thin and thick valves. It is also likely that in the clinical series there is an underestimate of the problem because few have died, clinical observation has only recognized the very severely affected, and unawareness of the possibility of the diffuse nature of the disease has prevented recognition in both clinical and pathological observations.

In conclusion, it is suggested that 'isolated' pulmonary valve stenosis often may be a misnomer, particularly in patients presenting with angiographic evidence of thick lumpy pulmonary valves subsequently found to be tricuspid, in infants with severe obstruction, and in children who show also stigmata of diffuse congenital abnormality outside the cardiovascular system. The tricuspid primordia of the pulmonary valve in this group suggests the possibility that the fetal injury may have occurred later in fetal growth and not necessarily in the early weeks of cardiac development. How often patients presenting with a thin domed pulmonary valve or a bicuspid pulmonary valve have truly 'isolated' pulmonary stenosis is as yet unknown.

We believe these concepts may apply to other apparently 'isolated' or simple congenital heart abnormalities and that some including pulmonary valve stenosis should be regarded as 'congenital cardiovascular disease'.

We acknowledge gratefully the constructive criticism of Dr. G. Farrer-Brown, Bland Sutton Institute of Pathology, Middlesex Hospital Medical School. Professor Reginald Hudson kindly allowed us to photograph the specimen illustrated in Fig. 5. We thank Mr. Donald Ross for permitting publication of his observations at operation, and Dr. Richard Emanuel for allowing us to examine his patient quoted in Table 3 and giving us access to the clinical information.

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Interaction between cardiovascular responses to sustained handgrip and Valsalva manoeuvre

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Interactions between the cardiovascular responses to the Valsalva manoeuvre and sustained handgrip were analysed in 5 men with untreated mild hypertension and 4 young normal subjects. Though set at a higher level, there was a normal blood pressure response to the Valsalva manoeuvre during concurrent sustained handgrip in 4 of the 5 hypertensive subjects. At the end of the handgrip period in which the Valsalva manoeuvres were performed, the blood pressure was higher and the heart rate lower than in the control period of sustained handgrip. The fifth subject developed a 'square wave' Valsalva response, which returned to a normal response when sustained handgrip was discontinued.

Analysis of RR interval changes in the normal subjects showed that both the tachycardia during, and the bradycardia after, the Valsalva strain period were significantly reduced during simultaneous sustained handgrip.

These results show that the two reflexes interact, but only to a minor extent, and that the baroreflex response is modified by sustained handgrip, rather than overridden as had previously been suggested. In view of the effect on the blood pressure and heart rate, subjects should avoid performing a Valsalva manoeuvre during sustained handgrip testing.

Because of the complexity of central nervous system integration of the different cardiovascular reflexes in man, effects attributed to one reflex response may often be modified by other reflexes acting at the same time. In the past, theoretical consideration has been given to this problem in relation to static (or sustained) muscular exercise, where there is a reflex increase in heart rate and blood pressure. Lind *et al.* (1964) and Freyschuss (1970) have both suggested that these reflex responses must override the baroreflex mechanism to allow the blood pressure and heart rate to rise together while sustained exercise continues. In practice, though most subjects taking part in sustained exercise testing are warned to avoid breath-holding or performing a Valsalva manoeuvre in case it interferes with the responses, there have been no studies published to show whether, in fact, there is any interaction between the two reflexes.

The present study was, therefore, designed to test whether or not there is any cardiovascular interaction between the response to the Valsalva manoeuvre and the response to sustained handgrip; and whether either response is modified by the other.

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Subjects and methods

Two groups were studied. In the first the intra-arterial blood pressure was measured directly in five asymptomatic male patients with untreated mild hypertension. Their ages ranged from 27 to 64 years. Apart from the blood pressure there were no abnormal physical signs. On investigation one subject was found to have a congenitally absent right kidney, and another a slightly enlarged heart on chest *x*-ray film. The patients had just completed a 24-hour period of intra-arterial radiotelemetry via an indwelling radial artery cannula (18 gauge, 6 cm Longdwel nylon). The telemetry apparatus was disconnected and the arterial cannula connected to a Statham P23 pressure transducer at a reference level 5 cm below the sternal angle and calibrated to the range of pressures in the patient under study. The frequency response to the catheter system was linear to 14 Hz. The arterial blood pressure and a continuous electrocardiograph were recorded onto ultraviolet paper using a Honeywell recorder (type 1185 Mark 2).

The second group of subjects consisted of 4 fit young men whose heart rates were recorded non-invasively onto magnetic tape and later analysed by a computer for accurate timing of the RR intervals. Details of the electrocardiographic recording technique have been previously described (Neilson and Vellani, 1972).

Static muscular exercise was performed using a standardized sustained handgrip test at 30 per cent

TABLE 1 *Blood pressure and heart rate responses to Valsalva manoeuvre before, during, and after period of sustained handgrip in 4 subjects with untreated mild hypertension (mean ± SD)*

	Pre-Valsalva period			*Phase I*			*Phase II*		
	Syst. BP (mmHg)	*Diast. BP (mmHg)*	*Heart rate (beats/min)*	*Syst. BP (mmHg)*	*Diast. BP (mmHg)*	*Heart rate (beats/min)*	*Syst. BP (mmHg)*	*Diast. BP (mmHg)*	*Heart rate*
Control I	156	73	83	182	98	87	109	71	107
	±13	±14	±23	±18	±11	±27	±17	±19	±26
Control II	156	69	85	180	91	86	115	78	109
	±13	±15	±28	±7	±17	±30	±23	±28	±28
1-min grip	176	87	90	203	114	93	119	80	107
	±19	±16	±23	±19	±14	±29	±23	±18	±25
2-min grip	199	95	100	222	112	95	134	90	112
	±17	±17	±19	±21	±17	±30	±28	±30	±29

Conversion factor from Traditional Units to SI Units: 1 mmHg≈0·133 kPa.

maximum voluntary contraction, as described previously (Ewing *et al.*, 1974). In most subjects this was sustained for approximately 4 minutes. The Valsalva manoeuvre was performed by blowing through a mouthpiece attached to a manometer and maintaining a pressure of 40 mmHg (5·3kPa) for 15 seconds. A side arm from the mouthpiece was connected to a pressure transducer. This signal was recorded on another channel on the ultraviolet recorder during the first study, and onto a second channel of the tape recorder in the second study, so that the onset and cessation of the Valsalva strain period could be accurately defined.

Statistical analysis was undertaken using Student's paired 't' test.

Plan of study

The method in the two studies was identical except that, in the second study, there was no control handgrip period. The nature of the studies was explained to the subjects and their consent obtained. The plan of each study was as follows:

(1) Supine rest period for 5 minutes.

(2) Sustained handgrip test at 30 per cent maximum voluntary contraction ('Handgrip I').

(3) Rest period for 15 minutes.

(4) Three successive Valsalva manoeuvres performed at 2-minute intervals ('Control I' refers to the mean values from the three manoeuvres).

(5) Rest period for 5 minutes.

(6) Sustained handgrip test at 30 per cent maximum voluntary contraction ('Handgrip II'). During this period a Valsalva manoeuvre was undertaken 1 minute after starting handgrip ('1-min grip'), and a second Valsalva 2 minutes after starting handgrip ('2-min grip').

(7) Rest period for 10 minutes.

(8) Three further Valsalva manoeuvres at 2-minute intervals ('Control II').

The phases of the Valsalva manoeuvre were defined as first documented by Hamilton, Woodbury, and Harper (1936) and more recently described by Cudkowicz (1968).

After the onset of straining, an initial increase in blood pressure occurs for 2 to 3 seconds (phase I), followed by a progressively decreasing blood pressure during continued strain (phase II). After the release of the strain, there is an initial further fall in blood pressure for a few seconds (phase III), followed by a rebound hypertension (the 'overshoot') (phase IV). The heart rate initially falls for 2 to 3 beats (phase I), then progressively increases during the strain (phase II), and increases further for a few seconds after release (phase III). Phase IV is marked by a bradycardia that follows shortly thereafter.

In the first study, the blood pressure during the different phases of the Valsalva manoeuvre was taken as the highest or lowest point during each phase, and the heart rate calculated from the simultaneous electrocardiogram. The heart rate changes were not measurable during phase III, and the systolic blood pressure exceeded the calibration range in one subject during phase IV; these results have, therefore, been omitted from the calculations. The other blood pressure and heart rate measurements during the first study were taken as the mean of 10 beats, either immediately before the onset of the manoeuvres, or just before release.

Though, in the second study individual RR intervals were measured, it was found that there was often considerable variation in the length of consecutive heart beats and, therefore, mean values were taken of the 10 beats before the onset of each Valsalva (pre-Valsalva period), of the 5 beats immediately before the end of the strain (phase II), and beats 11 to 20 after release of strain (phase IV). The onset of the phase IV bradycardia, though usually occurring around the tenth beat after the end of the strain period, was often difficult to define accurately in view of the variation in consecutive RR intervals. It usually continued for at least 20 beats and, therefore, the mean of beats 11 to 20 was chosen because it could easily be defined by reference to the simultaneous mouth pressure recording.

Phase III		*Phase IV*		
Syst. BP (mmHg)	*Diast. BP (mmHg)*	*Syst. BP (mmHg)*	*Diast. BP (mmHg)*	*Heart rate (beats/min)*
114	72	(217+)	106	65
±27	±23	—	±27	±10
101	63	(220+)	105	67
±19	±22	—	±25	±10
120	77	(233+)	117	79
±32	±28	—	±28	±23
147	90	(231+)	126	89
±19	±21	—	±24	±27

Results

1) Study 1 (intra-arterial blood pressure recording)

Four of the five subjects had normal responses to the Valsalva manoeuvre throughout the study, whereas the fifth subject behaved somewhat differently. His results have, therefore, been considered separately.

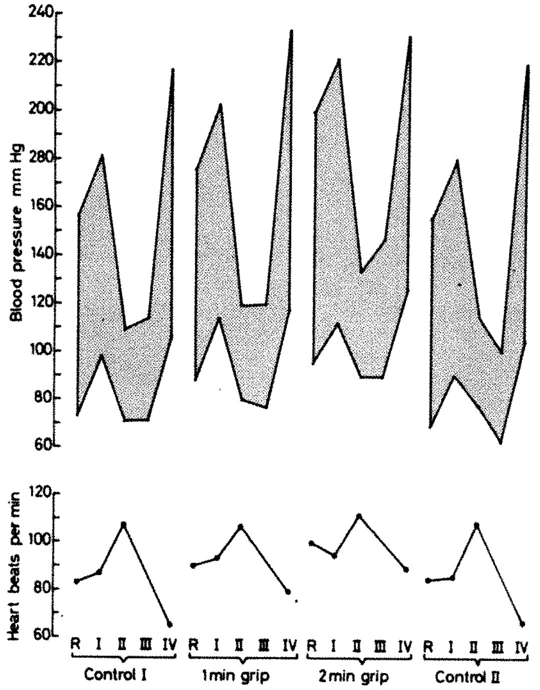

FIG. 1 *Blood pressure and heart rate responses (mean values) to Valsalva manoeuvre in 4 subjects with untreated mild hypertension before, during, and after period of sustained handgrip.*

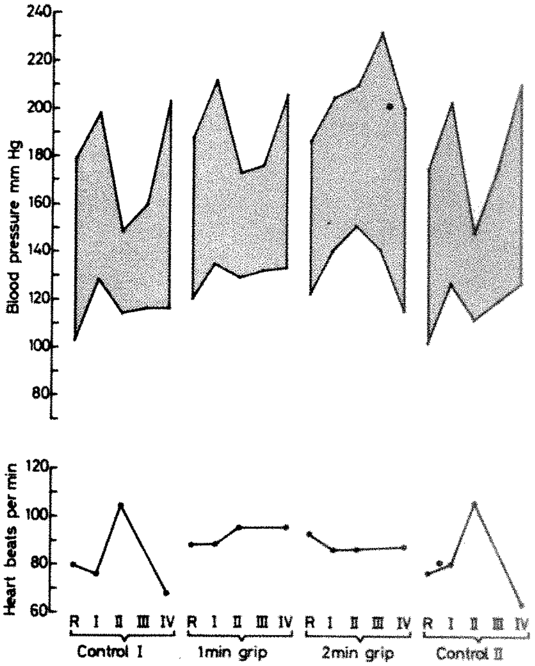

FIG. 2 *Abnormal response to Valsalva manoeuvre in one subject with untreated mild hypertension during period of sustained handgrip.*

A) Effect on Valsalva response

i) *Blood pressure responses* The results of the blood pressure changes during the different Valsalva manoeuvres are given in Tables 1 and 2 and Fig. 1. Mean values are given, as the responses were similar in all four subjects, and normal in pattern with the expected fall in pulse pressure during strain and overshoot in phase IV.

During the two control periods, the systolic and diastolic blood pressures were similar in all phases except for a small, but significant, difference in the resting diastolic blood pressure. During handgrip the systolic and diastolic blood pressures in the different phases of the Valsalva manoeuvre were all at a higher level than the control values. The differences were highly significant at 2-min grip, and less so at the 1-min grip period (Table 2), but the pattern of the Valsalva response was in no way altered. In particular, the blood pressure response during phase I and the overshoot in phase IV occurred to the same extent as in the control period.

There was, therefore, a normal blood pressure response to the Valsalva manoeuvre in all 4 subjects when this manoeuvre was performed concurrently

TABLE 2 *Blood pressure and heart rate responses to Valsalva manoeuvre: significant differences between results before, during, and after period of sustained handgrip (NS = not significant)*

	Pre-Valsalva period			*Phase I*			*Phase II*		
	Syst. BP	*Diast. BP*	*Heart rate*	*Syst. BP*	*Diast. BP*	*Heart rate*	*Syst. BP*	*Diast. BP*	*Heart rate*
Control I and control II	NS	$P<0{\cdot}001$	NS	NS	NS	NS	NS	NS	NS
Control I and 1-min grip	NS	$P<0{\cdot}05$	$P<0{\cdot}05$	NS	NS	$P<0{\cdot}02$	NS	NS	NS
Control I and 2-min grip	$P<0{\cdot}005$	$P<0{\cdot}001$	$P<0{\cdot}02$	$P<0{\cdot}001$	$P<0{\cdot}01$	NS	$P<0{\cdot}02$	NS	NS
1-min grip and 2-min grip	$P<0{\cdot}001$	NS	$P<0{\cdot}01$	NS	NS	NS	$P<0{\cdot}05$	NS	NS

with sustained handgrip, though it was set at a higher level.

ii) *Heart rate responses* (Tables 1 and 2 and Fig. 1) There were no significant differences in the heart rates during the Valsalva manoeuvre in either control period. During handgrip, the resting heart rates were faster, but there were no significant differences in the heart rate levels reached during phase II when compared with the control period. The heart rates in phase IV were faster both at 1-min grip (79 beats/min) and at 2-min grip (89 beats/min) than the bradycardia during control I (65 beats/min), but these differences did not reach statistical significance. There were corresponding reductions both in the tachycardia during strain (Control 1, 24 beats/min; 1-min grip, 17 beats/min; 2-min grip, 12 beats/min) and in the bradycardia after strain (control 1, 42 beats/min; 1-min grip, 28 beats/min; 2-min grip, 23 beats/min).

B) Effect on handgrip response (Table 3) The absolute level of blood pressure reached at the end of handgrip and the incremental rise were higher during handgrip II, but these differences did not reach a level of statistical significance. Likewise, the heart rate responses to handgrip were smaller during handgrip II, but they were only significant in the absolute level of heart rate reached during handgrip II (95 beats/min) when compared with handgrip I (102 beats/min $P<0{\cdot}05$).

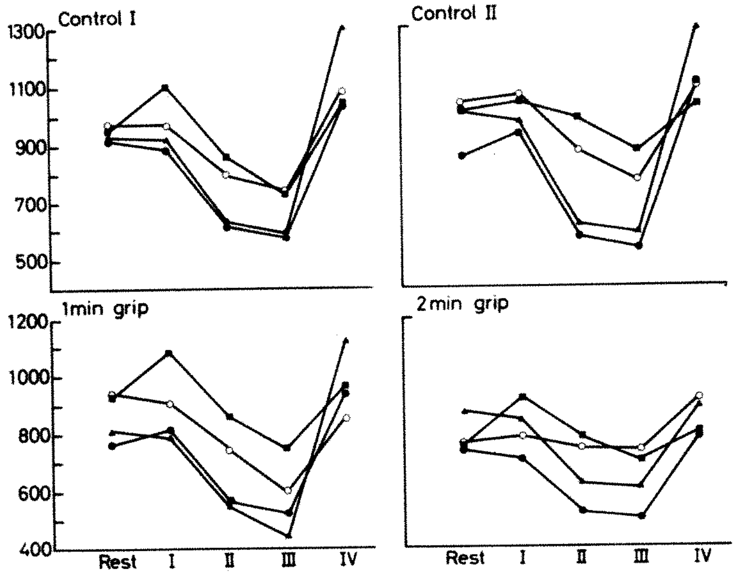

FIG. 3 *RR interval measurements (ms) in 4 normal subjects in different phases of Valsalva manoeuvres performed before, during, and after period of sustained handgrip.*

Phase III		*Phase IV*		
Syst. BP	*Diast. BP*	*Syst. BP*	*Diast. BP*	*Heart rate*
NS	NS	—	NS	NS
NS	NS	—	NS	NS
P<0·001	P<0·01	—	P<0·005	NS
NS	NS	—	NS	P<0·01

C) Abnormal response to combined handgrip and Valsalva manoeuvres (Fig. 2) One subject responded differently to the combined Valsalva and handgrip manoeuvres, though his control I Valsalva manoeuvre was normal in pattern. As can be seen from Fig. 2, during 1-min grip, he had a normal blood pressure response, but a flat heart rate response. During the 2-min grip period, he showed a 'square wave' blood pressure response, with no heart rate change. Control II, after release of handgrip, was again normal in pattern.

2) Study 2 (RR interval recordings)

In view of the heart rate changes noted during the intra-arterial studies, a more accurate analysis of the RR interval changes was undertaken in 4 normal subjects. The individual results are shown in Fig. 3, and the group results in Tables 4 and 5.

There were no consistent differences in the heart rate responses during the two control periods, except for a slightly longer RR interval in phase I during control II.

When the Valsalva manoeuvre was performed concurrently with sustained handgrip, the RR intervals were shorter than in the control period and these differences were statistically significant in all phases except phase III. The tachycardia (expressed as the pre-Valsalva RR interval minus phase II RR interval) during the strain period was reduced from 214 ms (control I) to 180 ms (1-min grip: NS) and 117 ms (2-min grip: P<0·005). After the release of the strain, the bradycardia (expressed as the phase IV RR interval minus phase II RR interval) was also reduced from 392 ms (control I) to 287 ms (1-min grip: P<0·01) and 182 ms (2 min grip: P<0·05).

Thus the heart rate response to the Valsalva manoeuvre is set at a higher level when it is performed during sustained handgrip; and both the tachycardia during, and the bradycardia after, the manoeuvre are attenuated.

Discussion

These results show that the blood pressure changes occurring during the Valsalva manoeuvre are not modified when sustained muscular exercise is performed concurrently. Though set at a higher level, the expected rises in blood pressure in phases I and IV, and falls in phases II and III occurred to the same degree whether or not sustained handgrip was being performed. The heart rate changes are, however, modified. The first study gave suggestive evidence of a diminished tachycardia during phase II and a smaller bradycardia in phase IV, and this was confirmed by the more accurate measurement of RR intervals in the second study.

In phase I of the Valsalva manoeuvre the increased blood pressure is the result of the increased intrathoracic pressure at the onset of straining; and the rapidly falling blood pressure during phase II is caused by the reduced venous return

TABLE 3 *Blood pressure and heart rate responses to sustained handgrip at 30 per cent maximum voluntary contraction; alone (handgrip I) and when Valsalva manoeuvres were performed (handgrip II) in 4 subjects with untreated hypertension (mean ± SD)*

	Rest			*30 per cent maximum voluntary contraction*			*Difference*		
	Syst. BP (mmHg)	*Diast. BP (mmHg)*	*Heart rate (beats/min)*	*Syst. BP (mmHg)*	*Diast. BP (mmHg)*	*Heart rate (beats/min)*	*Syst. BP (mmHg)*	*Diast. BP (mmHg)*	*Heart rate (beats/min)*
Handgrip I	160	74	84	209	104	102	49	30	18
	±22	±16	±25	±25	±20	±24	±24	±9	±8
Handgrip II	162	79	86	222	112	95	60	33	9
	±15	±13	±18	±18	±24	±25	±9	±14	±10
Significance	NS	NS	NS	NS	NS	P<0·05	NS	NS	NS

Conversion from Traditional Units to SI Units: 1 mmHg≈0·133 kPa.

TABLE 4 *RR interval measurements during Valsalva manoeuvres performed before, during, and after a period of sustained handgrip in four young normal male subjects (mean ± SD)*

	Pre-Valsalva period (ms)	*Phase I (ms)*	*Phase II (ms)*	*Phase III (ms)*	*Phase IV (ms)*	*Tachycardia during Valsalva (pre-Valsalva period—phase II) (ms)*	*Bradycardia after Valsalva (phase IV—phase II) (ms)*
Control I	938 ±24	971 ±99	724 ±125	650 ±87	1116 ±120	214 ±109	392 ±214
Control II	974 ±84	997 ±56	756 ±197	682 ±157	1120 ±111	218 ±154	364 ±282
1-min grip	859 ±84	900 ±134	679 ±150	577 ±128	966 ±110	180 ±82	287 ±227
2-min grip	779 ±61	809 ±91	662 ±121	631 ±110	844 ±61	117 ±145	182 ±117

producing a fall in cardiac output. In phase III the release of intrathoracic pressure and consequent rise in pulmonary vascular capacitance causes a momentary fall in cardiac output and further decrease in blood pressure. This is followed by the rebound hypertension or overshoot of phase IV, which is caused by the increase in cardiac output occurring at a point when the systemic vascular resistance is still raised in response to baroreflex stimulation produced by the fall in blood pressure during phase II.

The detectable reflex events during the Valsalva manoeuvre include the initial bradycardia in phase I, which is said to occur in response to the increased blood pressure (Elisberg, 1963; Stone, Lyon, and Teirstein, 1965; Fox *et al.*, 1966); but this was not consistently detected in the present study (Fig. 3). In phase II, tachycardia and peripheral vasoconstriction occur in response to the fall in blood pressure, if the baroreflexes are functioning normally, and there is then a bradycardia and peripheral vasodilatation in response to the blood pressure overshoot in phase IV.

Most young normal subjects (Lind *et al.*, 1964) and hypertensive patients without evidence of cardiac damage (Ewing *et al.*, 1973) increase their blood pressure during sustained handgrip by a heart rate dependent increase in cardiac output. Only in older normal subjects and in patients with myocardial dysfunction does a second mechanism, that of increased peripheral resistance by systemic vasoconstriction, come into play to raise the blood pressure (Macdonald *et al.*, 1966; Ewing *et al.*, 1973). The subjects in this study probably did not have any active peripheral vasoconstriction before the Valsalva strain period, and it is, therefore, likely that active peripheral vasoconstriction took place during the Valsalva strain period, thus explaining why the blood pressure overshoot occurred even though sustained handgrip was being performed concurrently.

One subject developed a 'square wave' response during sustained handgrip. This pattern of response to the Valsalva manoeuvre is found in cardiac failure where an increase in intrathoracic pressure does not critically reduce venous return with consequently little change in cardiac output during strain and, therefore, no baroreflex stimulation. Some work by Cudkowicz (1968) showed that infusion of noradrenaline will also produce a square wave response. Noradrenaline acts to produce a peripheral vasoconstriction and, though its effects on the venous side are not clear, there is an increase in central blood volume during infusion and right atrial filling pressure rises (Cudkowicz, 1968). During sustained muscular exercise, the venous

TABLE 5 *RR interval measurement during Valsalva manoeuvre: significant differences between results before, during, and after period of sustained handgrip (NS = not significant)*

	Pre-Valsalva period	*Phase I*	*Phase II*	*Phase III*	*Phase IV*	*Tachycardia during Valsalva*	*Bradycardia after Valsalva*
Control I and control II	NS	$P<0{\cdot}01$	NS	NS	NS	NS	NS
Control I and 1-min grip	$P<0{\cdot}05$	$P<0{\cdot}02$	$P<0{\cdot}05$	NS	$P<0{\cdot}005$	NS	$P<0{\cdot}01$
Control I and 2-min grip	$P<0{\cdot}05$	$P<0{\cdot}005$	$P<0{\cdot}05$	NS	$P<0{\cdot}005$	$P<0{\cdot}005$	$P<0{\cdot}05$
1-min grip and 2-min grip	NS	NS	NS	NS	NS	NS	NS

pressure and tone increase (Seaman *et al.*, 1973) and, in those subjects who raise their blood pressure by increasing systemic vascular resistance, these two factors may combine to increase the effective venous return and prevent the throttling effect of the raised intrathoracic pressure during the Valsalva strain period on the blood vessels within the thorax. The conditions would then be fulfilled for the square wave response and the baroreflex would not be brought into play. Though there are no studies yet available, it seems likely that, in patients with impaired left ventricular function whose response to handgrip is abnormal (Helfant, DeVilla, and Meister, 1971; Kivowitz *et al.*, 1971), the superimposition of a Valsalva manoeuvre onto a sustained handgrip test would produce a square wave response. This combined handgrip/Valsalva manoeuvre may prove useful as a further sensitive test for detection of left ventricular dysfunction.

The significant reduction, both in the tachycardia of phase II and the bradycardia of phase IV, during simultaneous Valsalva and handgrip manoeuvres despite similar blood pressure changes, shows that there is modification of the reflex responses during the Valsalva manoeuvre in phases II and IV. Cunningham *et al.* (1972) showed that there was reduction of baroreflex sensitivity during sustained handgrip and this present study supports his view. There is, however, no evidence to support the view that the baroreflexes are actually overriden during sustained handgrip (Lind *et al.*, 1964; Freyschuss, 1970). It is rather that a modification of the baroreflex responses occurs as indicated by the alterations in heart rate during the simultaneous Valsalva manoeuvre. The bradycardia of phase IV was still sufficient to lower the heart rate to a level below the immediate pre-Valsalva period both at 1 minute and at 2 minutes of sustained handgrip, thus showing that the reflex was active in phase IV despite continued sustained handgrip. A similar conclusion was reached by Bergman, Campbell, and Wildenthal (1972), who found that the 'diving' reflex persisted during concurrent sustained handgrip.

Many investigators have noted that their subjects were instructed to avoid a Valsalva manoeuvre during sustained handgrip tests (Freyschuss, 1970; Krayenbuehl *et al.*, 1972, 1973; Nutter, Schlant, and Hurst, 1972; Fisher *et al.*, 1973; Grossman *et al.*, 1973; Payne, Horwitz, and Mullins, 1973; Ludbrook, Karliner, and O'Rourke, 1974; Stefadouros *et al.*, 1974a, b) but none has documented the effect that the Valsalva has on the handgrip response. This study now provides these data and shows that, if a Valsalva manoeuvre is performed near to the end of a period of sustained handgrip, the blood pressure at the end of handgrip may be higher, and the heart rate lower, than a control period where no Valsalva manoeuvre is performed. This probably reflects the phase IV overshoot in addition to the blood pressure rise caused by the sustained handgrip alone. Similarly, the phase IV bradycardia probably contributes to the lower heart rate recorded at the end of the handgrip II period. Warnings to avoid a Valsalva manoeuvre during sustained handgrip testing are, therefore, justified.

The cardiovascular responses to the Valsalva manoeuvre and sustained handgrip have been shown by this study to be modified by each other, but only in a minor way. There is no evidence to suggest that either reflex response is dominant over the other or has an 'overriding' effect. These reflex responses are two of a large number of vascular reflexes that, though not directly interacting, are all elegantly integrated within the whole pattern of central nervous system control of the cardiovascular system.

We thank Professor K. W. Donald for his help and encouragement.

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Left ventricular function after aortic valve replacement[1]

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Changes in haemodynamics and in systolic time intervals, early after aortic valve replacement, were studied in a group of 15 patients. Though all the haemodynamic measurements were within normal limits at 44 hours after operation, there was a persistent change in systolic time intervals (shortening of left ventricular ejection time and electromechanical systole, and prolongation of pre-ejection period and increase in the ratio PEP/LVET). The effect of periods of myocardial ischaemia during cardiopulmonary bypass on myocardial function is suggested as the explanation for the changes observed.

Haemodynamic changes in the early postoperative period after open heart surgery have been previously reported (Austen *et al.*, 1966; Carey and Plested, 1972; Fordham and Resnekov, 1967; Kirklin and Theye, 1963; Kloster *et al.*, 1966; Rastelli and Kirklin, 1967. The variable period of reduced cardiac output after cardiopulmonary bypass is influenced by many factors and as a result interpretation of events is difficult. The extent of the effects of bypass and of the ensuing changes in left ventricular performance still remains to be defined. The atraumatic technique of systolic time interval measurement has been used widely in preoperative clinical assessment of left ventricular function, and in some later postoperative studies (Benchimol and Matsuo, 1971; Bonner, Sacks, and Tavel, 1973; Gibson, Broder, and Sowton, 1970; Parisi, Salzman, and Schechter, 1971; Weissler, Lewis, and Leighton, 1972). This report concerns its use in combination with routine haemodynamic measurements in the early period after aortic valve surgery.

Patients and methods

Fifteen patients (14 men, 1 woman) undergoing routine elective aortic valve replacement were studied. The mean age was 48 years with a range from 24 years to 68 years. Clinically, 8 patients had predominant aortic regurgitation and 3 aortic regurgitation alone. The aetiology was rheumatic in 7 patients, congenital in 5, bacterial endocarditis in 2, and syphilis in 1.

Normothermic cardiopulmonary bypass was used with a Hartmann haemodilution prime and a Temptrol bubble oxygenator (Bentley Laboratories). Bilateral coronary perfusion was used with intermittent ischaemic periods of up to 15 minutes. The mean bypass time was 101 minutes (range from 65 to 176 minutes), and mean ischaemia time was 23 minutes (range from 6 to 45 minutes). In eight patients the aortic valve was replaced by a Starr-Edwards prosthetic valve (model 1260), and in 7 patients by a homograft (antibiotic nutrient preservative as described by Al-Janabi and Ross, 1973).

All patients remained in sinus rhythm throughout the study. No inotropic agents were used in the postoperative period, except for 3 patients who were taking digoxin before operation and afterwards. Serum potassium was monitored and supplements given to maintain serum levels between 4·0 and 5·5 mmol/l. None of the patients required intermittent positive pressure ventilation for more than three hours after operation. There were no hospital deaths and no evidence of myocardial damage was found in the postoperative electrocardiograms.

The preoperative non-invasive study was performed during the afternoon before operation, and the haemodynamic values were measured in the anaesthetic room, before the induction of anaesthesia, after premedication with papaveretum (20 mg) and hyoscine (0·4 mg). All studies were repeated 4, 20, and 44 hours after operation.

The systolic time intervals were determined from the electrocardiogram (lead chosen to show Q wave), the phonocardiogram (usually at the left sternal edge where aortic valve closure (A_2) is most clearly recorded), the external carotid pulse tracing, and respiratory tracing, simultaneously recorded

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on an Elema-Schönander Mingograf 34. The following time intervals were measured: electromechanical systole (Q-A$_2$) and left ventricular ejection time (LVET). The pre-ejection period (PEP) was calculated by subtracting LVET from Q-A$_2$ and the PEP/LVET ratio was calculated (Weissler *et al.*, 1972); these measurements were corrected for heart rate and sex: Q-A$_2$ index, LVET index, and PEP index were derived using the regression equation from normals (Weissler, Harris, and Schoenfeld, 1968). As an alternative method of expression, deviation from normal was shown as percentage of predicted value which takes heart rate and sex into account (Weissler and Garrard, 1971).

An arterial cannula was inserted percutaneously into the brachial or radial artery, and a Swan-Ganz catheter into the brachial vein for right heart and pulmonary arterial wedge pressures. After the operation, in addition, a direct left atrial line was left *in situ*, and a venous cannula was placed in the right atrium through the innominate vein. All the pressures were recorded on a Devices M4 Recorder, using Bell and Howell pressure transducers, with the mid-thorax as the reference zero. Cardiac output was measured using the cardiogreen dye-dilution technique, with injection of the dye into the right atrium or pulmonary artery and sampling from the arterial cannula. The reported values are the average of two consecutive determinations. Calculation of forward stroke work index (SWI) was by the following formula:

$$\text{SWI}=\text{PSAP}\times\text{SI}\times13{\cdot}6$$

where PSAP is the peak systolic arterial pressure (mmHg), and the SI is forward stroke index (ml/beat per m^2 BSA). This value underestimates total left ventricular stroke work in the presence of aortic regurgitation because it does not take into account the regurgitant volume, and in the presence of aortic stenosis because it ignores the aortic valve gradient.

TABLE 2 *Systolic time intervals before and after aortic valve replacement*

	Before operation	*After operation**		
		4 hours	*20 hours*	*44 hours*
PEP index† (ms)	113·5 ±11·36	168·5 ±10·76 P<0 0005	163·5 ±18·79 P<0·0005	157·5 ±18·09 P<0·0005
LVET index† (ms)	437·1 ±23·92	360·2 ±19·83 P<0·0005	348·1 ±19·42 P<0 0005	350·5 ±30·34 P<0·0005
Q-A$_2$ index† (ms)	550 8 ±28 35	531·3 ±18·04 P<0 025	511·5 ±22·65 P<0·0005	514·8 ±25·17 P<0 0005
PEP/LVET†	0·271 ±0·036	0·715 ±0·150 P<0·0005	0·661 ±0 123 P<0·005	0·641 ±0·136 P<0·005

*P values indicate significance of differences between postoperative and preoperative measurements.
†Mean ± SD.

Student's *t*-test was used for the analysis of the results.

Results

I: Haemodynamic data (Table 1)

Right atrial and left atrial pressures did not change significantly during the study. Mean arterial pressure was within normal limits and showed no significant change.

Heart rate increased significantly from the preoperative value throughout the postoperative period, while the cardiac index was reduced postoperatively at 4 hours after operation (P<0·001).

TABLE 1 *Haemodynamic variables before and after aortic valve replacement*

	Before operation	*After operation**		
		4 hours	*20 hours*	*44 hours*
Right atrial pressure (mmHg)	6 2±2·3	7·1±3·4	7·1±2·4	7·2±2·5
Left atrial pressure (mmHg)	11·2±8 0	10·4±5·1	11·2±4·4	10·7±5·9
Mean arterial pressure (mmHg)	84·9±15·1	91·7±15·0	84·4±14·7	90·1±11·9
Heart rate (beats/min)	76 8	99·8 P<0·001	88·6 P<0·005	101·4 P<0 001
Cardiac index (l/min per m^2 BSA)	3·08±0·77	2·22±0·37 P<0·001	2·62±0·50	2·91±0·65
Stroke index (ml/beat per m^2 BSA)	40·9±10·0	23·2±5·7 P<0·001	30 3±5·6 P<0 005	28·6±5·9 P<0·001
Systemic arterial resistance (units)	15·0±4·0	21·4±6·9 P<0·005	16·7±5 1	17 4±3·9
Left ventricular stroke work index (g m/beat per m^2 BSA)	81·8±23·7	40·4±11·9 P<0·001	49·2±15·6 P<0·005	48·20±13 0 P<0·005

*P values indicate significance of differences between postoperative and preoperative measurements.
Conversion factors from Traditional to SI units: 1 mmHg≈0·133 kPa; 1 unit≈8 Mpa s m^{-3}.

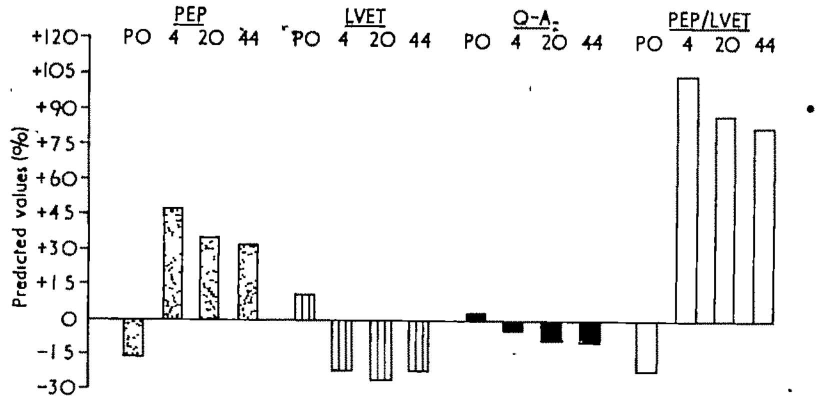

FIG. 1 *Systolic time intervals as percentages of predicted values (Weissler et al., 1968) before operation, and at 4, 20, and 44 hours after operation. PEP, pre-ejection period; LVET, left ventricular ejection time; $Q\text{-}A_2$, total electromechanical systole; PO, preoperative.*

Stroke index was decreased throughout the postoperative period of the study and systemic arterial resistance was increased at 4 hours after operation ($P < 0.005$). Stroke work index was high preoperatively and decreased significantly ($P < 0.005$) to normal values throughout the postoperative period.

Comparing patients who before operation had aortic stenosis with those who had aortic regurgitation, there was no significant difference in these haemodynamic variables and there was no significant difference in postoperative behaviour between patients with Starr-Edwards prosthetic valves and those with aortic homografts (all P values > 0.05).

II: Systolic time intervals

The mean values for the systolic time intervals corrected for heart rate and sex are shown in Table 2. Before operation PEPI is short and LVETI and $Q\text{-}A_2I$ are prolonged. The ratio PEP/LVET is also shorter than normal. In the postoperative period PEPI was prolonged and LVETI was shortened; the ratio PEP/LVET was longer than normal and significantly different from the preoperative values. The most abnormal results were seen 4 hours after operation. In Fig. 1, the histograms of the percentages of the predicted values are shown at the four different times of study in all the patients for PEP, LVET, $Q\text{-}A_2$, and PEP/LVET.

Statistical comparison of the group of patients with aortic stenosis before operation with the group with aortic regurgitation, and of the group with Starr-Edwards prostheses with the group with homograft valves, showed no significant differences. The most sensitive variable, PEP/LVET, was correlated with duration of myocardial ischaemia during cardiopulmonary bypass, and with the total bypass time. In Fig. 2, PEP/LVET at 44 hours is plotted against total bypass time and ischaemic time during operation. Fig. 2b shows that there was no close correlation between total bypass time and PEP/LVET at 44 hours in 15 patients ($r=0.601$; SEE 16·9). On the other hand, there was a close correlation between ischaemic time and PEP/LVET ($r=0.923$; SEE 3·71). Further analysis suggested two populations: three patients with ischaemic time less than 10 minutes, and the other 12 patients for whom the correlation between ischaemic time and PEP/LVET was very close ($r=0.977$; $y=20.20x+133.55$) (Fig. 2a).

Discussion

After aortic valve replacement most patients had a normal cardiac index within 24 hours, despite the fact that some were limited functionally by their heart disease before operation; previous reports have shown little difference in the early postoperative haemodynamics between patients with predominant aortic stenosis and those with predominant aortic regurgitation (Austen *et al.*, 1966). Routine haemodynamic monitoring of patients undergoing open heart surgery usually includes measurement of right and left ventricular filling pressures and systemic arterial pressure for 24 to 48 hours after operation in order that complications including heart failure and tamponade can be recognized early and prevented; in addition, cardiac output is often measured. However, these observations do not provide a comprehensive assessment of left ventricular performance. Recently, invasive techniques have been used for the

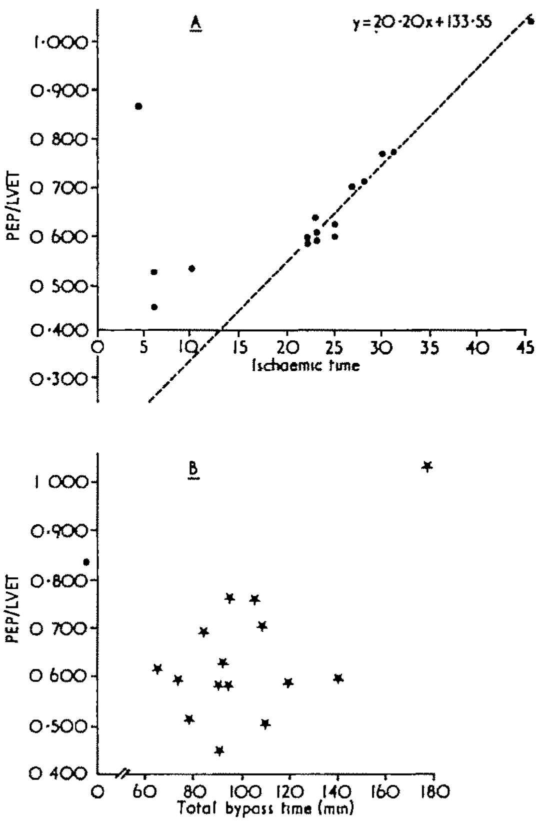

FIG. 2 *(a) Myocardial ischaemic time (min) plotted against pre-ejection period/left ventricular ejection time ratio. Regression equation* $y=20{\cdot}20x+133{\cdot}55$ *is calculated omitting 3 patients with ischaemic times of less than 10 minutes. Correlation coefficient* $r=0{\cdot}977$*; SEE 1·31. PEP, pre-ejection period; LEVET, left ventricular ejection time. (b) Total cardiopulmonary bypass time (min) plotted against pre-ejection period/left ventricular ejection time ratio. Correlation coefficient* $r=0{\cdot}601$*; SEE 16·9. PEP, pre-ejection period; LVET, left ventricular ejection time.*

assessment of haemodynamic changes during this period, employing catheter tip manometers left in the ventricular cavity (Bolooki, 1973), and electromagnetic flowmeters placed around the aorta (Morrow, Brawley, and Braunwald, 1965; Chamberlain *et al.*, 1974). Systolic time intervals have been shown to correlate well with other measurements of left ventricular performance (Garrard, Weissler, and Dodge, 1970), and are well suited for serial records on individual patients: use of systolic time intervals in the early postoperative period is appropriate provided that they are combined with routine measurements of left ventricular pump function.

In our group of patients cardiac index and stroke index were low at 4 hours but progressively improved towards 44 hours after operation, changes that have also been shown by others (Austen *et al.*, 1966; Kloster *et al.*, 1966; Rastelli and Kirklin, 1967). Systemic arterial resistance is increased after open heart surgery, and is probably the result of an increase incirculating catecholamines (D. C. Fluck, 1973, personal communication); Rastelli and Kirklin (1967) thought that this was the result of the essentially nonpulsatile flow during cardiopulmonary bypass. We believe that the reduced cardiac index four hours after valve replacement is caused by myocardial depression, as shown by the depression of stroke work index without change in left atrial pressure. As calculated stroke work index is an underestimate in patients with aortic regurgitation, a fall in this index after regurgitation has been abolished by valve replacement is an important observation.

Systolic time intervals are known to be altered in patients with aortic valve disease. When heart failure is absent, there is prolongation of left ventricular ejection time and of electromechanical systole and shortening of the pre-ejection period (Benchimol and Matsuo, 1971; Parisi *et al.*, 1971; Weissler *et al.*, 1972). This was also found in our group of patients before operation; there was no significant difference between patients with aortic stenosis and those with aortic regurgitation. Prolongation of LVET is thought to be caused by increased afterload in aortic stenosis and by increased left ventricular stroke volume in aortic regurgitation (Ahmed *et al.*, 1972; Parisi *et al.*, 1971; Weissler *et al.*, 1972). PEP shortening in aortic valve disease is closely related to the difference between aortic and left ventricular end-diastolic pressures divided by the maximal rate of rise of left ventricular pressure (Parisi *et al.*, 1971). The ratio PEP/LVET is independent of heart rate and sex and has been widely used as a single expression of ventricular performance (Weissler *et al.*, 1968, 1972). After operation there is a complete reversal of the preoperative changes, and this was highly significant ($P<0{\cdot}005$). Though the dramatic haemodynamic changes following correction of aortic valve defects would be expected to return the STI to normal, these changes are more profound and are similar to those found in heart failure (Weissler *et al.*, 1968). It is of interest that these changes persist when the cardiac index and stroke work index have returned to normal. Parisi *et al.* (1971) and Benchimol and Matsuo (1971) studied their patients one week to three months after aortic valve repair or Starr-Edwards valve replacement, and Rothlin and Gattiker (1973) studied a group of patients 24 hours after aortic valve replacement with fascia lata or Björk-Shiley valves. All found prolongation of pre-ejection period and shortening of left ventricular ejection time and electromechanical systole; Rothlin and Gattiker also showed that these changes were independent of changes in the cardiac index, which was then low, and that the changes in systolic time intervals correlated well with the duration of the period of ischaemic hypothermic cardiac arrest. Our data confirms their results (Fig. 2).

However, other factors must be considered in the appreciation of these changes in the systolic time intervals after operation. Dependence of systolic time intervals on preload and afterload is well known (Ahmed *et al.*, 1972; Weissler *et al.*, 1972). In our group of patients, preload assessed by left atrial pressure did not change. Afterload was relatively constant after operation but clearly the changes from the preoperative values were different in aortic stenosis and aortic regurgitation. Left ventricular pump performance, as judged by cardiac index and stroke work index, was within normal limits at 44 hours after operation in this study, but systolic time intervals remained abnormal suggesting that there was persisting depression of left ventricular function.

The effects of anaesthesia are unlikely to explain these changes in systolic time intervals. Anaesthetic agents are known to depress left ventricular performance, and to decrease LVET and Q-A$_2$ and prolong PEP during induction of anaesthesia (Blackburn *et al.*, 1973), but no prolonged effect has been shown. Catecholamine release is also known to alter the systolic time intervals in a similar manner to that shown here (Harris, Schoenfeld, and Weissler, 1967), but is accompanied by haemodynamic changes which have not been shown in our patients beyond 4 hours after operation. Lastly, the effect of cardiopulmonary bypass on myocardial function remains a possible explanation. It has been shown both experimentally and in man that there are deleterious effects of cardiopulmonary bypass on myocardial metabolism and structure that could account for the persistence of abnormalities in some of the variables commonly measured to assess ventricular function (Benzing *et al.*, 1970; Braimbridge *et al.*, 1973; Darracott *et al.*, 1973; Isom *et al.*, 1973; Jenkins, Branthwaite, and Bradley, 1973; Stemmer *et al.*, 1973). Thus using systolic time intervals, we have shown an impairment of left ventricular performance up to 44 hours after aortic valve replacement, whereas this is not apparent beyond 4 hours after operation with routine methods of assessment of left ventricular pump function. Furthermore, the effects upon the myocardium of the periods of ischaemia used during cardiopulmonary bypass could explain this observation; this is supported by the close correlation between the ischaemic period during bypass and PEP/LVET 44 hours after operation (Fig. 2a). Cardiopulmonary bypass alone, without ischaemia, is shown in Fig. 2b to be unlikely to be a significant factor. Though the abnormality of PEP/LVET suggests myocardial depression, correlation of this finding with conventional invasive measures of left ventricular function is at present lacking.

Further studies on this subject will be necessary to clarify the influence of cardiopulmonary bypass and intermittent myocardial ischaemia on myocardial metabolism and function, and the relation between the altered systolic time intervals and more sophisticated measurements of left ventricular function.

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Second heart sound after pulmonary arterial banding operation

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After a pulmonary arterial banding procedure the phonocardiograms of 38 patients were correlated with haemodynamic and angiographic findings. Twenty-four patients had uncomplicated ventricular septal defect, 2 had single ventricle, 5 had transposition of the great arteries, 5 had atrioventricular canal defects, and 2 had coarctation of the aorta and ventricular septal defect. P_2 *was separated from* A_2 *by less than 40 ms in 10 of the 11 patients with high pulmonary vascular resistance. Of 27 patients with nearly normal pulmonary vascular resistances and distal pulmonary artery pressures less than 50/20 mmHg (6·7/2·7 kPa),* 24 had* A_2-P_2 *intervals of over 40 ms. A narrow* A_2-P_2 *interval with a satisfactory band was found in 2 patients with large right-to-left shunts.* A_2-P_2 *interval did not change appreciably with age, and this measurement is a useful guide as to the effectiveness of pulmonary artery banding by one year after operation. If this interval is less than 40 ms, repeat catheterization should be carried out as such patients may have persisting pulmonary hypertension and an increased pulmonary vascular resistance.*

Most patients have an easily heard splitting of the second heart sound (S_2) after a successful pulmonary banding. Some of the clinical reviews of the banding procedure fail to mention this change in the second heart sound (Dammann *et al.*, 1961; Stark *et al.*, 1969), while others (Takahashi *et al.*, 1968) have noted this splitting of the second sound as a characteristic clinical finding after banding. Aziz, Mesko, and Ellison (1972) stressed the potential value of the changes of the second heart sound after banding and presented data showing that with low pulmonary arterial pressures distal to the band, the split was over 40 ms while, if the pulmonary arterial pressure was raised, the splitting interval was less than 40 ms. This observation indicated that the phonocardiogram could serve as a non-invasive method for monitoring pulmonary arterial pressures after banding. However, only 17 subjects were studied by the above authors, all but 2 with adequate bands, and all subjects were over 2 years of age. Patients with pulmonary arterial banding have been followed with phonocardiograms for about 15 years at Winnipeg Children's Hospital. The phonocardiographic, haemodynamic, and angiographic findings of 38 banded patients are reviewed to assess the validity of using the phonocardiogram as a guide to the effectiveness of the banding procedure in reducing distal pulmonary arterial pressure.

Subjects and methods

Only patients in severe distress had pulmonary arterial banding. All had failed to respond to medical treatment. Several were desperately ill at the time of banding and the operation was performed in the presence of heart failure and lung infection. Only those patients who had post-banding cardiac catheterizations with measurement of distal pulmonary arterial pressure and with phonocardiograms obtained within a few months of catheterization are included in the present report. The 38 patients comprise about two-thirds of all the patients banded over a 15-year period. Twenty-four patients had uncomplicated ventricular septal defect, 2 had single ventricle, 5 patients had complete atrioventricular canal defects, 5 had transposition of the great arteries, and 2 had coarctation of the aorta as well as ventricular septal defect. The amount of constriction applied at operation was based on the cardiac response to banding

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and on the distal pulmonary arterial pressure (measured by pressure transducer in 33 patients and estimated by palpation in the others). An attempt was made to reduce the pulmonary arterial systolic pressure to about 40 mmHg (5·3 kPa). The mean band diameter was 7 mm, some infants developed striking cardiac slowing, with reduction of the PA pressures to 40 mmHg (5·3 kPa) and the surgeon accepted a lesser degree of constriction.

An index of pulmonary blood flow was obtained by using the pulmonary/systemic flow ratio. As an index of pulmonary vascular resistance, the pulmonary/systemic resistance ratio was calculated using mean pulmonary arterial and femoral arterial pressures. Serial film angiography was performed on all patients and measurements were obtained as indicated in Fig. 1. The minimal diameter of the pulmonary arterial segment underlying the band was measured; the distance from the pulmonary valve ring to the proximal part of the band, as well as the diameters of the pulmonary valve ring and of the aortic valve ring, were recorded. The average magnification factor in the angiographic system was 1·11, and was about the same for each subject, so that the measurements were not corrected for this distortion. Phonocardiograms were obtained using a Maico microphone at the left sternal edge in the second left intercostal space, using the Electronics for Medicine DR8 recorder in the 120-500 Hz range. The degree of splitting was obtained by averaging the intervals between the aortic and pulmonary components of S_2 (A_2-P_2 interval) for 5 consecutive heart beats. In addition, the height of P_2 divided by the height of A_2 was obtained to provide an index of the relative intensities of these sounds. Recorder speed was 75 or 100 mm/s. In children aged 3 years and over a carotid pulse curve was used to confirm the identification of A_2 (Fig. 2).

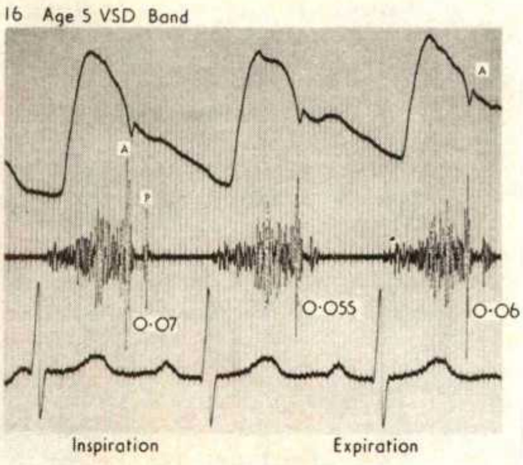


FIG. 2 *Case 16—slight change in A_2-P_2 interval with respiration. 100 mm/s paper speed, 20 ms time lines. Use of carotid pulse to identify A_2. Sharpest and highest deflections arbitrarily used for timing A_2 and P_2.*

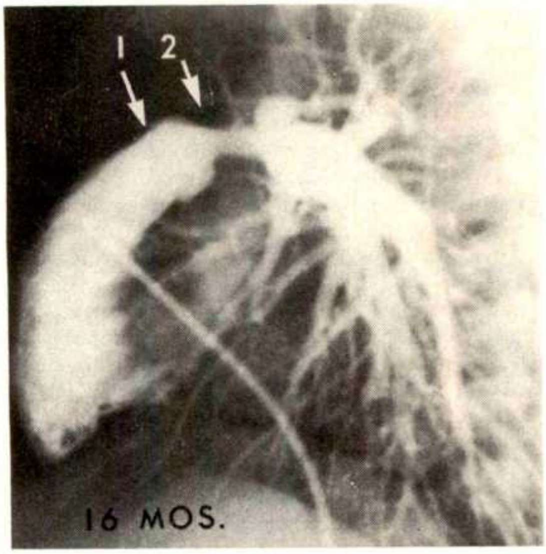


FIG. 1 *Angiocardiogram. Arrow 1 = plane of pulmonary valve; arrow 2 = level of band. Distance between arrows is distance of band above pulmonary valve ring.*

Results

Of the 38 patients, 15 were 2 years of age or younger, and the oldest patient was 9 years old. The mean age was 4±3 years. Individual data are listed in Table 1.

The lumen of the pulmonary artery under the band was <10 mm in 29 of the 38 subjects, and <7 mm in 16 subjects. The systolic pulmonary arterial pressure was >50 mmHg (6·7 kPa) in 7 patients; 5 of these had banded segment diameters of 10 mm or more. The pulmonary/systemic resistance ratio was >0·30 in 11 patients and >0·60 in 5 of these. In 3 of these latter 5 patients, the banded segment was 10 to 14 mm in diameter.

Fig. 3A depicts the relations between raised pulmonary artery pressures or pulmonary vascular resistances (expressed as the resistance ratio), and A_2-P_2 intervals, and Fig. 3B shows similar findings for the ratio of the intensity of P_2/A_2. The values 0·30 for resistance ratio and 50/20 mmHg (6·7/2·7 kPa) pulmonary arterial pressure were chosen arbitrarily. Of the 11 patients with resistance ratios of 0·30 or more, the A_2-P_2 interval was < 30 ms in 7, 36 to 38 ms in 3, and 45 ms in 1 patient. Of the 8 patients with pulmonary arterial pressures >50/20 mmHg (6·7/2·7 kPa), A_2-P_2 was < 40 ms in 7. Of the 14 patients with A_2-P_2 intervals < 40 ms, 11 had raised pulmonary arterial pressures and/or pulmonary vascular resistances (arbitrary values given above). Of the 24 patients with A_2-P_2 intervals of 40 ms or greater, only 1 had a resistance ratio >0·30, and/or pulmonary arterial pressure >50/20 mmHg (6·7/2·7 kPa).

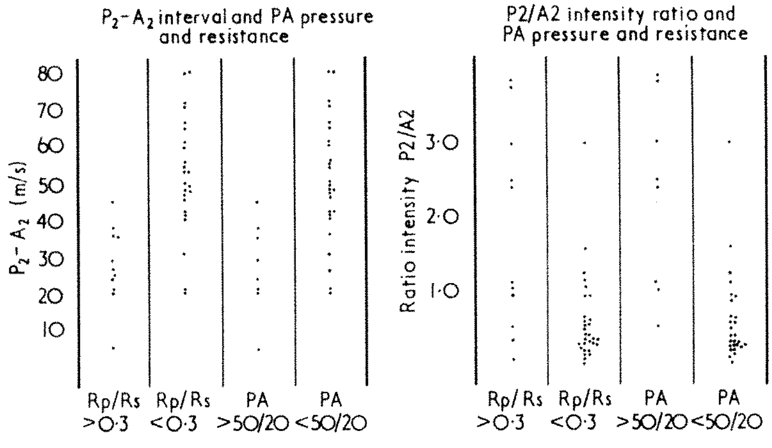
The pulmonary component of the second sound was of relatively greater intensity in patients with pulmonary hypertension, but the dividing line between those with raised pulmonary arterial pressures and resistances was less distinct for the ratio of P_2/A_2 intensity than it was for A_2-P_2 interval. Of the 11 subjects with RP/RS ratios >0·30, 8 had P_2/A_2 intensity ratios of 1·0 or greater. Of the 27 patients with resistance ratios below 0·30, 22 of the subjects had P_2/A_2 intensity ratios < 1·0. There were similar findings for those subjects with pul-

TABLE 1 *Haemodynamic, angiographic, and phonocardiographic data*

Case No.	*P_2-A_2 (ms)*	*Age (y)*	*Qp/Qs*	*Rp/Rs*	*Band (mm)*	*Band/ aorta ratio*	*Band distance (mm)*	*Systolic gradient (mm)*	*PA pressure (mmHg)*			*Desaturation (%)*	*P_2/A_2*	*RR (ms)*	*Lesion*
									S	*D*	*M*				
1	5	4	0·78	1·11	11	0·85	15	10	85	45	75	9	5·10	605	VSD
2	29	2	0·83	0·95	6	0·40	15	64	46	24	36	24	1·02	546	VSD
3	20	5	0·74	1·21	10	0·56	22	15	105	45	70	11	6·62	773	VSD
4	40	2	1·00	0·27	7	0·47	50	72	22	14	16	8	0·58	420	VSD
5	56	1	0·69	0·19	5	0·31	8	80	12	7	9	6	0·25	448	VSD
6	48	2	0·97	0·21	6	0·60	15	70	22	10	15	8	0·25	395	VSD
7	66	4	1·53	0·12	8	0·38	17	73	22	10	16	0	0·31	468	VSD
8	72	5	1·47	0·25	10	0·42	30	62	34	11	20	4	0·40	669	VSD
9	65	4	0·65	0·25	9	0·50	12	80	20	8	13	1	0·10	560	VSD
10	50	5	1·40	0·23	10	0·48	12	77	38	12	27	10	3·00	628	VSD
11	20	4	0·70	0·15	6	0·35	17	92	15	9	11	10	1·58	642	VSD
12	24	6	1·25	0·64	14	0·74	18	17	80	35	60	17	2·40	746	VSD
13	21	1	1·33	0·13	6	0·27	18	56	20	8	13	20	1·13	400	VSD
14	38	8	1·81	0·32	15	0·79	13	12	83	28	47	1	2·50	560	VSD
15	80	5	1·14	0·15	7	0·50	23	60	24	10	14	5	0·57	540	VSD
16	71	4	1·22	0·16	4	0·19	9	74	23	8	14	1	0·28	600	VSD
17	41	1	1·30	0·25	7	0·47	11	54	36	12	24	6	0·40	388	VSD
18	46	1	0·71	0·27	4	0·33	11	80	15	6	12	21	0·22	448	VSD
19	48	1	0·72	0·18	4	0·41	15	74	14	7	9	8	0·65	494	VSD
20	49	2	2·20	0·10	7	0·42	10	64	26	11	18	20	0·95	410	VSD
21	61	2	0·89	0·17	4	0·32	9	85	15	7	10	7	0·50	495	VSD
22	53	4	0·92	0·16	8	0·43	15	63	17	7	11	6	0·24	694	VSD
23	27	4	0·48	0·35	8	0·40	16	86	21	12	17	15	1·00	486	VSD
24	33	4	1·39	0·17	6	0·25	21	63	27	9	18	1	1·20	438	VSD
25	54	3	2·31	0·19	9	0·45	18	33	47	17	32	2	1·08	773	AVC
26	80	5	1·00	0·14	12	0·36	30	83	20	8	14	16	0·35	545	AVC
27	55	5	1·70	0·13	8	0·34	20	82	28	10	15	10	0·32	739	AVC
28	36	2	0·54	0·32	4	0·27	2	70	20	7	13	11	0·14	360	AVC
29	21	3	1·64	0·33	8	0·43	16	35	55	22	35	8	3·11	396	AVC
30	55	8	1·90	0·17	8	0·44	4	50	40	15	25	10	0·14	620	SV
31	47	1	1·25	0·18	7	0·35	13	63	22	10	14	3	0·21	413	SV
32	25	8	0·83	0·40	5	0·31	17	45	37	11	22	25	0·35	607	TGA
33	36	9	1·56	0·38	11	0·46	15	57	58	26	48	22	0·54	672	TGA
34	35	7	0·57	0·29	6	0·32	12	85	17	10	12	50	0·05	520	TGA
35	45	2	0·61	0·75	6	0·32	7	51	54	30	38	42	1·12	480	TGA
36	60	1	0·90	0·28	6	0·39	16	120	15	8	12	21	0·31	533	TGA
37	43	2	0·79	0·26	4	0·21	17	104	31	11	20	1	0·96	507	COA
38	42	5	1·00	0·18	10	0·67	30	48	18	8	13	0	0·65	613	COA
Means	45	4	1·12	0·32	7	0·42	15	63	33	14	23	11	1·07	542	
SD	±17	±3	±0·46	±0·27	±2	±0·15	±6	±24	±22	±10	±16	±11	±1·40	±116	

Age—at time of heart catheterization and phonocardiogram; Qp/Qs—pulmonary/systemic flow ratio; Rp/Rs—pulmonary/systemic resistance ratio; band/aorta—ratio of band diameter to aortic valve diameter; P_2/A_2—ratio of peak phonocardiographic deflections of P_2 to A_2; PA pressure: S = systolic, D = diastolic, M = mean; desaturation—pulmonary vein oxygen saturation (or 96%) minus arterial; VSD—ventricular septal defect; AVC—atrioventricularis communis; SV—single ventricle; COA—coarctation of aorta (plus VSD); TGA—transposition of great arteries. Cases 32 and 33 also had SV.

Conversion from Traditional to SI units: 1 mmHg ≈ 0·133 kPa.



(A) (B)

FIG. 3 *(A) A_2-P_2 interval in patients divided into those with high or low pulmonary vascular resistance and those with high or low pulmonary artery pressures. (B) Ratio of intensity of P_2/A_2 in patients divided into those with high or low pulmonary vascular resistance and those with high or low pulmonary artery pressures.*

monary hypertension defined as pulmonary arterial pressure >50/20 mmHg (6·7/2·7 kPa).

Four patients had both short A_2-P_2 intervals and P_2/A_2 intensity ratios >1·0, yet had low pulmonary arterial pressures and resistances. Two of these patients had right-to-left shunts of 16 and 29 per cent of systemic flow.

The ratio of pulmonary to systemic blood flow was >1·5 in 8 patients. This was not associated with a greater degree of splitting of the second heart sound compared with those with little or no left-to-right shunt. The pulmonary arterial pressure was >40/20 mmHg (5·3/2·7 kPa) in 5 of these 8 patients and less than this value in the other 3.

The band was >15 mm above the valve in 17 patients, and 11 of these were over 3 years of age. The band was <10 mm above the valve in 6 patients and 4 were less than 3 years of age.

Arterial oxygen desaturation was calculated by subtracting the systemic arterial oxygen saturation from the pulmonary venous oxygen saturation. In 14 of the subjects, pulmonary venous saturations were obtained (mean value 96%); in the remaining 24 subjects it was assumed that pulmonary venous saturation was 96 per cent. Indicator dilution curves revealed a trace or greater right-to-left shunt in the majority of patients. The desaturation of arterial blood was greater than 8 per cent saturation in 10 of the 24 subjects with uncomplicated ventricular septal defects. In 4 of these 10 subjects the right-to-left shunt was associated with pulmonary hypertension and increased pulmonary vascular resistance, while in the remaining 6 subjects the right-to-left shunt was apparently caused by the narrowness of the band.

Representative phonocardiograms are shown in Fig. 4 to 7. Fig. 4 illustrates the variability in A_2-P_2 intervals and P_2/A_2 intensity ratios in 3 patients with adequate bands. Case 35 with transposition of the great arteries had an A_2-P_2 interval exceeding 40 ms, but had raised pulmonary arterial pressures. Fig. 5 shows the very loud P_2 in 2 patients with severe residual pulmonary hypertension. Of 15 patients with phonocardiograms at age 2 to 3 years, and subsequently at least 2 years later at age 4 to 6 years, the mean A_2-P_2 interval changed from 40 to 45 ms ($P > 0·10$) while RR interval changed from 565 to 570 ms ($P < 0·05$). There seemed to be little change with age, for the A_2-P_2 interval increased by over 10 ms in only 3 of the 14 subjects, and the mean values at the two ages were not significantly different. In Fig. 5, Case 25 showed a wider A_2-P_2 interval with age, and Case 10 no change.

Some respiratory variation may occur in the A_2-P_2 interval after PA banding. The largest variation occurred in Case 38, in whom spontaneous closure of a large ventricular septal defect had occurred during the first year. This girl had an associated coarctation of the aorta, which was not repaired at the time of banding but was electively repaired at age 7 along with removal of the band. At cardiac catheterization at age 5, the right ventricular pressure was 66 mmHg (8·8 kPa), systolic pulmonary arterial pressure 18 mmHg (2·4 kPa), and left ventricular pressure 134 mmHg (17·8 kPa). The most notable feature of S_2 was the pronounced

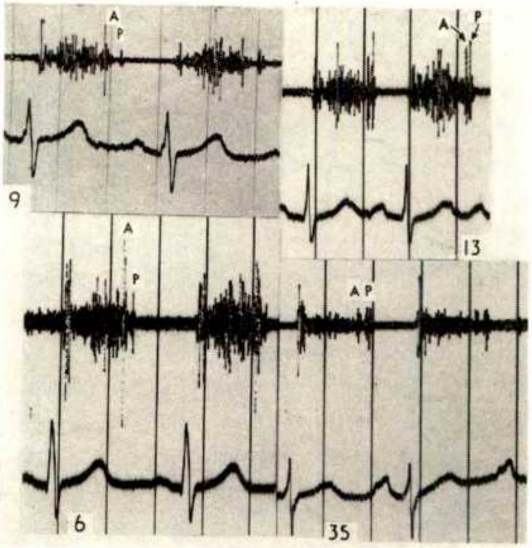


FIG. 4 *Phonocardiograms from 4 banded patients. Case 9 at age 4, Case 13 at age 1, Case 6 at age 2 years, all with large ventricular septal defects and normal PA pressures. Variable degrees of splitting of S_2, variable ratio of intensities of P_2/A_2. Case 35 has transposition of the great arteries and systolic PA pressure was 54 mmHg (7·2 kPa). Time lines 0·2 s in these and subsequent phonocardiograms.*

respiratory fluctuation in the A_2-P_2 interval (Fig. 6). In most of the remaining subjects the A_2-P_2 intervals were either constant or changed by < 10 ms with different phases of respiration. No attempt was made to control respiration during the phonocardiograms on these patients, the majority of whom were under 5 years of age.

Linear regression analyses were carried out for the A_2-P_2 interval and the P_2/A_2 intensity ratios (Table 2). The highest correlation was for pulmonary arterial diastolic pressure and sound intensity ratio, and other significant correlations were found between resistance ratio, the ratio of band diameter to aortic diameter, and systolic pressure gradient across the band.

Discussion

As experience is gained in operating on small infants with large ventricular septal defects, considerably fewer pulmonary arterial banding procedures will be performed. None the less, in some complex cardiac anomalies, such as single ventricle, transposition of the great arteries, and atrioventricular canal, the banding procedure is likely to remain a useful palliative procedure. It is in some of these patients that it may be difficult to enter the pulmonary artery at catheterization and an indirect means of assessing the pulmonary haemodynamics after banding would be most useful. In the series reported here, 4 patients had an inadequate band. Two of these subjects subsequently had pulmonary systemic resistance ratios of greater than 1·0, and are considered inoperable. In one subject the pulmonary/systemic resistance ratio was 0·64 and successful closure of the ventricular septal defect was carried out, but four years after operation the patient was in difficulty because of progressive pulmonary vascular disease. While 2 of these 4 patients moved away and were not seen again for 2 to 3 years after the banding procedure, and the parents of a third patient refused further operation, the phonocardiogram correctly identified these subjects as having persisting pulmonary hypertension and might have allowed earlier reinvestigation and effective surgery.

While the correlation between the level of pulmonary arterial pressure or pulmonary vascular resistance and the A_2-P_2 interval was not high, measurement of this interval was of practical importance. All but one of the subjects with a significant increase in pulmonary vascular resistance (pulmonary/systemic resistance ratio >0·30) had an A_2-P_2 interval of less than 40 ms, allowing a recognition of 90 per cent of subjects with an increase in resistance. Of the 27 subjects with normal resistances, 3 had A_2-P_2 intervals of < 40 ms, a frequency of 11 per cent false positive identification of patients likely to have an increased pulmonary vascular resistance by using the 40 ms cutoff value.

The ratio of the intensity of P_2/A_2 was a less reliable index of rise in pulmonary arterial pressures or vascular resistance than was the A_2-P_2 interval. Of subjects with an increased pulmonary vascular resistance, 73 per cent had P_2/A_2 sound intensity ratios < 1·0, resulting in a false negative index in 27 per cent of the subjects. Eighteen per cent of the subjects gave a false positive result having P_2/A_2 ratios of < 1·0, in the absence of any increase in pulmonary arterial pressure or pulmonary vascular resistance.

One explanation of why the patient with a low pulmonary arterial pressure distal to an adequate band has wide splitting of the second heart sound is that the pulmonary valve does not close until the proximal pulmonary artery pressure falls from its high systolic level to a low diastolic value.

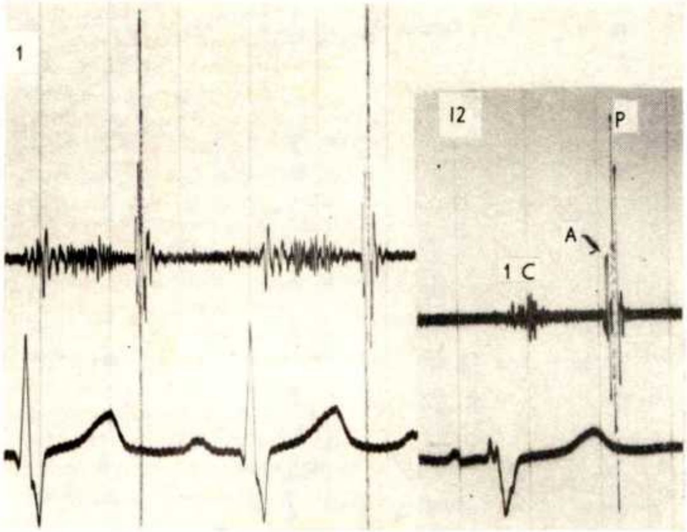


FIG. 5 *Two patients with unsatisfactory results with severe persisting pulmonary hypertension. Case 1—very loud single S_2; Case 12—systolic ejection click (C), P_2 is much louder than A_2 and A_2-P_2 is only 24 ms.*

Shaver *et al.* (1974) recently showed that the P_2 sound is delayed 33 to 89 ms beyond that point at which pulmonary arterial pressure falls below right ventricular pressure. Recognition of this time lag (called hangout) was possible with the development of practical catheter tip manometers. It was reported that the wide splitting of the second sound in patients with idiopathic dilatation of the pulmonary artery, mild pulmonary stenosis, and atrial septal defect, was not the result of prolonged right ventricular systole, but of an increase in this 'hangout' interval. Values for this 'hangout' interval will be of use in inderstanding the wide A_2-P_2 interval in patients with pulmonary arterial banding, but are not available. A reduced pulmonary arterial capacitance present in patients with pulmonary arterial banding might shorten the A_2-P_2 interval by reducing the P_2 'hangout' while a prolonged right ventricular systole and a low pulmonary arterial diastolic pressure would tend to delay pulmonary valve closure. Other factors likely to modify the A_2-P_2 interval include heart rate, distance of the band above the pulmonary valve ring, age, pulmonary blood flow and its ratio to systemic flow, magnitude of right-to-left or left-to-right shunts, closure of the ventricular defect, and respiration. The same subject was not compared at different heart rates, but no correlation was found between the A_2-P_2 interval and heart rates of different subjects. Aziz *et al.* (1972) reported an inverse linear correlation between the distance the band was above the pulmonary valve ring and the A_2-P_2 interval, but this correlation was not confirmed in the present study. Age seemed to influence this distance in our patients. Age would also influence the relative degree of constriction produced by the

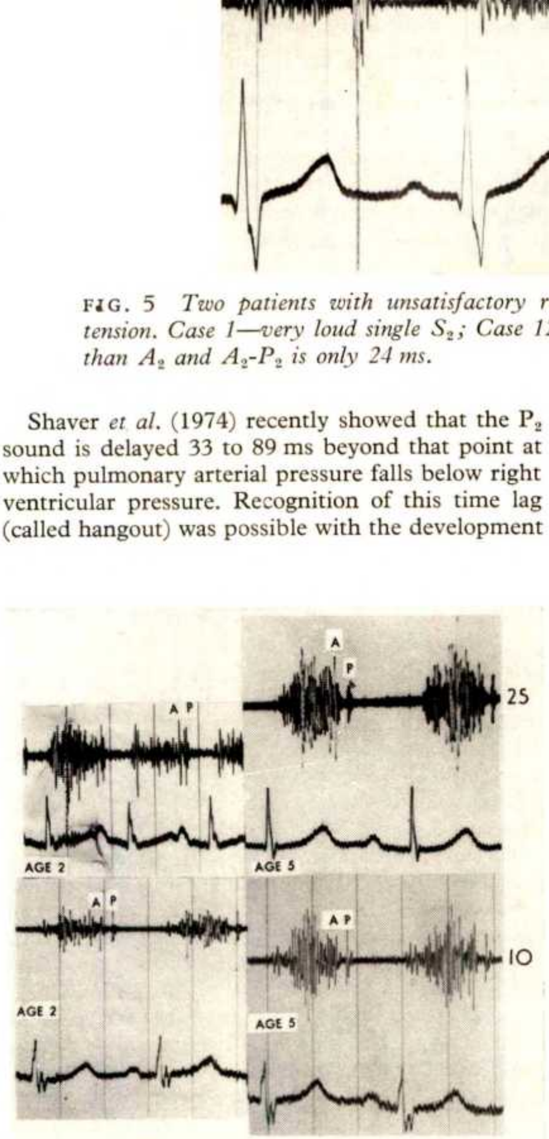


FIG. 6 *Phonocardiograms 3 years apart in 2 patients. Case 25—A_2-P_2 increased from 26 to 52 ms. Case 10—A_2-P_2 changed very little from 52 to 50 ms.*

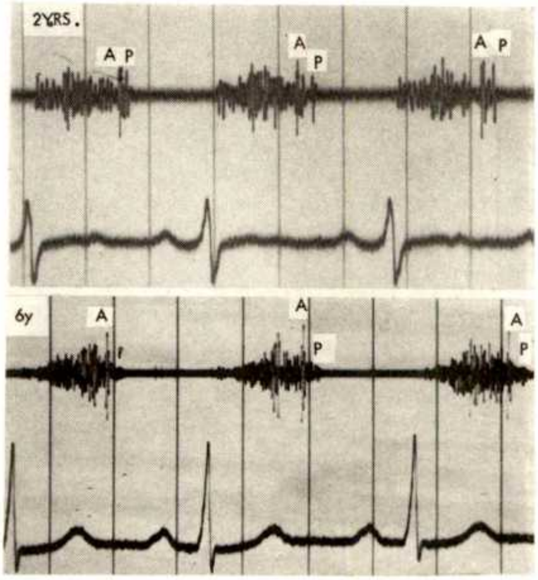


FIG. 7 *Phonocardiograms—Case 38 at age 2 and 6 years. There is a striking respiratory variation in the A_2-P_2 interval. The patient had coarctation of aorta and the ventricular defect closed spontaneously.*

band, for presumably the band remains fixed while other structures increase in size.

In addition, age might influence pulmonary vascular resistance, and, if previously high, some recession might be expected on the basis of anatomical studies (Dammann *et al.*, 1961). There was no strong correlation between the pulmonary/systemic flow ratio and the A_2-P_2 interval in our clinical material except that a short A_2-P_2 interval was found in 2 subjects with normal pulmonary arterial pressures and large right-to-left shunts. The reduced pulmonary flow in these patients might lead to a shortening of right ventricular systole.

TABLE 2 *Correlation coefficients A_2-P_2 and P_2/A_2*

	A_2-P_2 *All patients (38)*	A_2-P_2 *VSD only (26)*	P_2/A_2 *All patients (38)*
Qp/Qs	0·18	0·19	—
Rp/Rs	–0·58*	–0·64*	0·73*
Band width	–0·10	–0·30	0·45*
Band/aortic diameters	–0·31	–0·44*	0·54*
Band distance	0·14	–0·01	0·16
Systolic gradient	0·49*	0·54*	–0·63*
PA diastolic pressure	–0·58*	–0·66*	0·81*
Arterial oxygen desaturation	–0·29	–0·53*	–0·06
RR interval	–0·02	–0·17	0·33*

*$P < 0·05$.

Conversion from Traditional Units to SI Units: 1 mmHg≈ 0·133 kPa.

Most of the patients studied by Aziz *et al.* (1972) were over 4 years of age. The important time to know whether a band has achieved the desired result of lowering pulmonary arterial pressures is within 6 to 12 months of creating the band and before there has been any progression of pulmonary vascular disease. The data on the patients presented here suggest that phonocardiography with the measurement of A_2-P_2 interval is an excellent guideline as to the effectiveness of the band, even at age 1 to 2 years. Patients who have A_2-P_2 intervals less than 40 ms one year after banding should have repeat catheterization studies in order to reassess their haemodynamic situation.

All but three patients were operated on by Dr. Colin C. Ferguson, Director of Department of Surgery, Health Sciences Children's Centre of Winnipeg. Some of the measurements were carried out by Dr. Milton Gold. I am also grateful to Dr. V. Chernick, Chairman of Department of Pediatrics, University of Manitoba, for reviewing the manuscript.

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Familial centronuclear myopathy associated with 'cardiomyopathy'

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Two cases of familial centronuclear myopathy are described. Both presented features of 'cardiomyopathy and one had signs of slight congenital aortic stenosis. The 'cardiomyopathy' was fatal in one case. The clinical histological, and necropsy findings are presented and discussed.

In 1966, the first case of a congenital myopathy, histologically characterized by the presence of central nuclei in 85 per cent of the skeletal muscle fibres was reported (Spiro, Shy, and Gonatas, 1966). After this report, a number of identical cases were described and the general descriptive term of centronuclear myopathy was proposed (Sher *et al.,* 1967). Though the presence of cardiac abnormalities was mentioned in some cases, no clear description of these findings has been given.

The purpose of the present report is to describe the cases of two brothers with centronuclear myopathy associated with evidence of 'cardiomyopathy'.

Case reports

Case 1

The older of two brothers was born in 1957 after a normal pregnancy and delivery. His parents were in good health and there was no family history of any particular disease. The patient had difficulty in sucking, started walking late, and during childhood tired easily. After several weeks of increasing dyspnoea, he was admitted to our hospital at the age of 15 years.

The heart rate on admission was 140 beats/min and the systolic blood pressure 70 mmHg (9·3 kPa), with unrecordable diastolic blood pressure. There was striking distension of the neck veins, and the liver was enlarged to 3 cm below the costal margin, but there was no peripheral oedema. The heart was enlarged to the left and a diffuse left ventricular impulse was felt. Auscultation of the heart showed a summation gallop but no murmurs. Fine inspiratory râles were heard over the bases of both lungs. Both heart chambers were enlarged on the chest *x*-ray (Fig. 1). The electrocardiogram showed first degree atrioventricular block, extreme left axis deviation, and possible left atrial hypertrophy (Fig. 2a). The vectocardiogram showed left anterior hemiblock and intra-atrial conduction disturbances.

Further clinical examination showed generalized muscle weakness and wasting, a waddling gait, winging scapulae, lumbar hyperlordosis, dorsal kyphoscoliosis, and slight bilateral ptosis of the eyelids (Fig. 3). Standing up from the supine position was impossible without the use of arms and hands. The tendon reflexes were weak or absent. Cutaneous sensibility and tests for cerebellar function were normal. His intelligence was normal.

Electromyography of the main muscle groups of the thigh and lower leg indicated only minor non-specific alterations. Over both temporal zones a theta arrhythmia with paroxysms during hyperventilation was found on the electroencephalogram. *X*-ray studies of the skeleton showed that the anterior arch of the atlas bone was absent. Routine biochemical studies, including determination of creatine phosphokinase, aldolase, and creatinuria, were normal. No autoimmune antibodies were present. The vital capacity of the lungs was 1·6 l and the 1 s forced expiratory volume 1·4 l, a restrictive pattern probably caused by muscle weakness. The karyotype was normal.

The signs of heart failure disappeared under treatment with digitalis, diuretics, and a sodium-free diet. The cardiac enlargement, however, persisted.

A biopsy of the right anterior tibial muscle revealed on histological examination a considerable variation in the diameter of the fibres, ranging from 10 to 80 μ. A few isolated small fibres showed regressive changes, like microvacuoles, or signs of regeneration (basophilia with vesicular nuclei). Short nuclear chains and small thick nuclear clumps were seen in some fibres. Of 500 muscle fibres examined in transverse section, 74 per cent presented central nuclei (Fig. 4a). This number varied between 30 and 92 per cent according to the examined field. Inflammatory changes, endomysial sclerosis or fat infiltration were not present. Spindles, nerves, and blood vessels had a normal aspect. The glycogen and protein contents of the muscle were within normal limits. Histochemically a pronounced, numerical predominance of type I fibres was found. Most type II fibres were atrophied (Fig. 4b).

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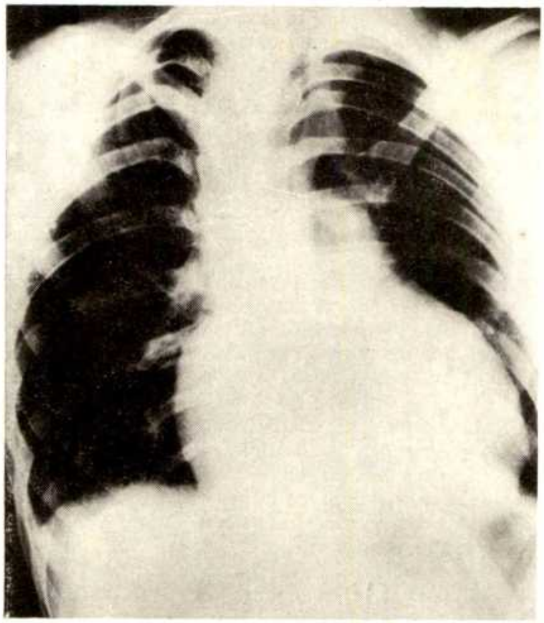

FIG. 1 *Chest x-ray of Case 1 shows obvious cardiomegaly and scoliosis.*

At the age of 16, the patient presented progressive heart failure and was readmitted with pulmonary oedema and unrecordable blood pressure. The electrocardiogram was unchanged, except for a sinus tachycardia of 140/min. Chest *x*-ray examination showed pulmonary oedema and further progression of the cardiac enlargement. The patient perished three days after admission as a consequence of extreme left heart failure, which did not respond to digitalis and diuretics.

At necropsy, the heart was extremely dilated, with displacement of both lungs. On gross examination the pericardium appeared normal and contained a small amount of serous fluid. The heart weighed 450 g. The right atrium, right ventricle, and left ventricle were very dilated. The thickness of the right ventricular wall was 2 to 3 mm and the left ventricular wall 7 to 10 mm. All heart valves had a normal appearance. No mural thrombi were present. The coronary and pulmonary arteries and the aorta were normal. Microscopical examination (Fig. 5) of the myocardium revealed extensive fibrosis in both heart chambers. Though this fibrosis occurred throughout the entire thickness of the myocardium, it was particularly dominant around the blood vessels. Some myocardial fibres showed hypertrophy without attenuation. No degenerative changes were found. The endocardium was slightly thickened (mean thickness at the level of the left ventricular outflow tract: 20–50 μ, and of the right ventricular outflow

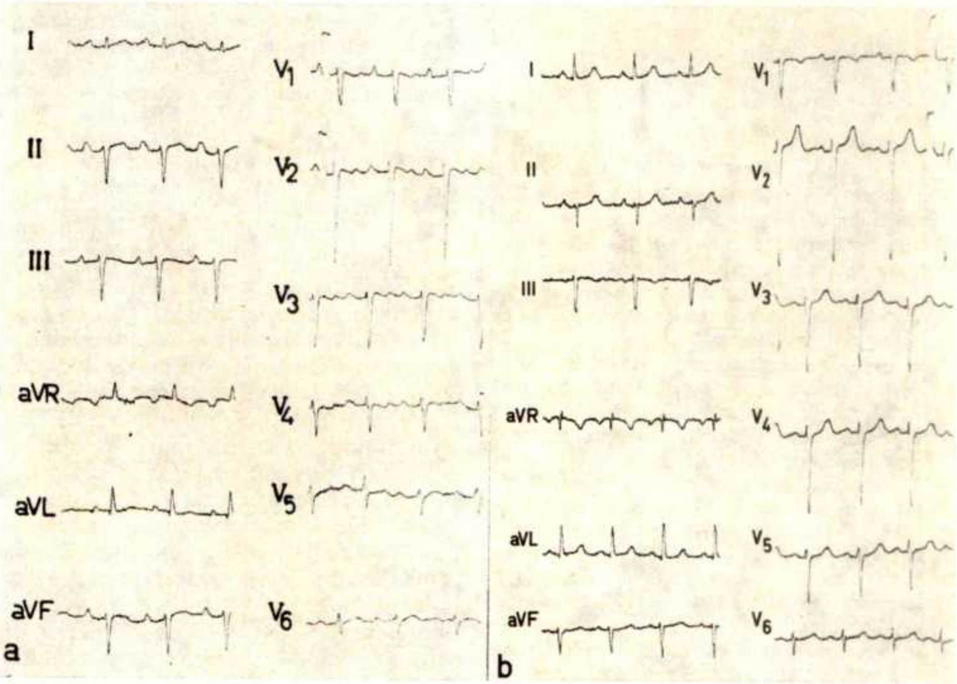

FIG. 2*a) Electrocardiogram of Case 1 shows first degree atrioventricular block, extreme left axis deviation, and an rS pattern in the chest leads across to V6. b) Electrocardiogram of Case 2: left axis deviation and chest lead pattern similar to that of Case 1.*

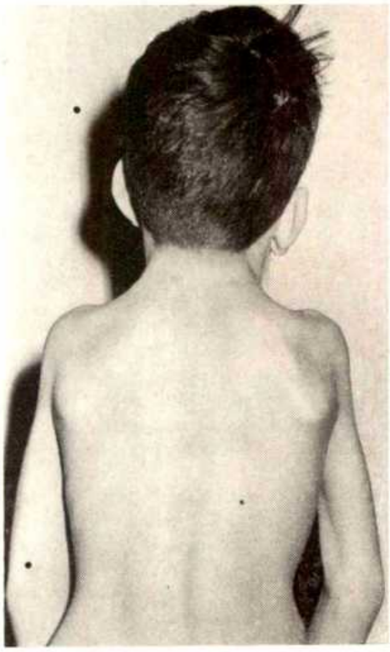

FIG. 3 *Case 1: muscular atrophy of the shoulder girdle and winged scapulae.*

tract: 10–30 μ). The pericardium presented a completely normal aspect. No microscopical examination of the conducting system was made.

Case 2

The second brother was born in 1959. He also had difficulty in sucking and started walking at the age of 4 years. Mild congenital valvular aortic stenosis was suspected at the age of 6 years, but the left ventricular ejection time measured on a carotid pulse recording, the electrocardiogram, the chest *x*-ray film, and right heart catheterization were normal.

At the age of 14 years, after the death of his older brother, he was admitted to our hospital. He presented the same general pattern of muscle wasting and weakness as his older brother, but somewhat less pronounced.

Neurological examination revealed a myopathic gait. Achieving the standing position was impossible without the aid of arms and hands. There was also a striking lumbar lordosis and dorsal kyphoscoliosis. The tendon reflexes were weak or absent. Cutaneous and deep sensitivity were normal as were the cerebellar tests. Speech was difficult for the letters G, K, B, and R. Intelligence was normal.

The serum creatine phosphokinase was 420 units (upper limit of normal: 55 units). Serum transaminases and aldolase were normal. The karyotype was normal. No autoimmune antibodies were found. Physical examination of the heart showed slight cardiac enlargement and the signs of mild valvular aortic stenosis.

The heart was moderately enlarged on a chest *x*-ray film. The left ventricular ejection time was now 110 per cent. The electrocardiogram (Fig. 2b) was completely altered: extreme left axis deviation of −50° was present without any evidence of left ventricular hypertrophy. The vectocardiogram showed the pattern of a left anterior hemiblock. Electromyography showed a typical myopathic pattern. An *x*-ray survey of the skeleton showed an absent anterior arch of the atlas bone. The electroencephalogram was slightly disturbed by a diffuse slow arrhythmia.

A biopsy of the anterior tibial muscle was performed. On microscopical examination the diameter of the muscle fibres varied from 10 to 60 μ. The smaller basophilic fibres were not grouped but dispersed, and isolated basophilic fibres with vesicular nuclei were seldom found. In some fibres the number of myofibrils was reduced and the sarcoplasm presented focally or diffusely granular or hyaline alterations. The most prominent feature was the internal location of nuclei in 66 per cent of 400 fibres examined on transverse sections. This percentage varied from 61 to 71 when the fibres were examined in groups of 50. Some fibres also contained long nuclear chains and thickened nuclear clumps. In some areas a slight endomysial fibrosis and rare fat cells were found. Histochemically, type I fibres were predominant in number but generally smaller than type II fibres. Internal nuclei were present in both type I and II fibres.

The patient has been seen every 6 months at the outpatient department. No special treatment, except for a sodium-free diet, has been instituted. Until now he has been doing well and no progression of his muscular or cardiac abnormalities has occurred.

Discussion

With rare exceptions (Vital *et al.*, 1970), centronuclear myopathy is clinically characterized by slow and progressive wasting and weakness of the skeletal muscles beginning at birth. Ptosis of the eyelids is present in the majority of the reported cases. Hypo- and areflexia are constant findings. The only biochemical abnormality reported in some patients is a rise in the level of serum creatine phosphokinase. Electromyography is usually normal or reveals atypical abnormalities, which do not permit a distinction between pathological processes of the peripheral nerves or muscle fibres; on the other hand it can show a myopathic pattern as in our Case 2. The electroencephalogram is usually disturbed and seizures were reported in two cases (Coleman *et al.*, 1968; Sher *et al.*, 1967). The central or internal location of nuclei in a high percentage of the fibres is the dominant histological abnormality. A pronounced variation of the diameter of the muscle fibres is often found. Necrosis is almost absent; sometimes discrete fibrosis and fat infiltration are observed as in our

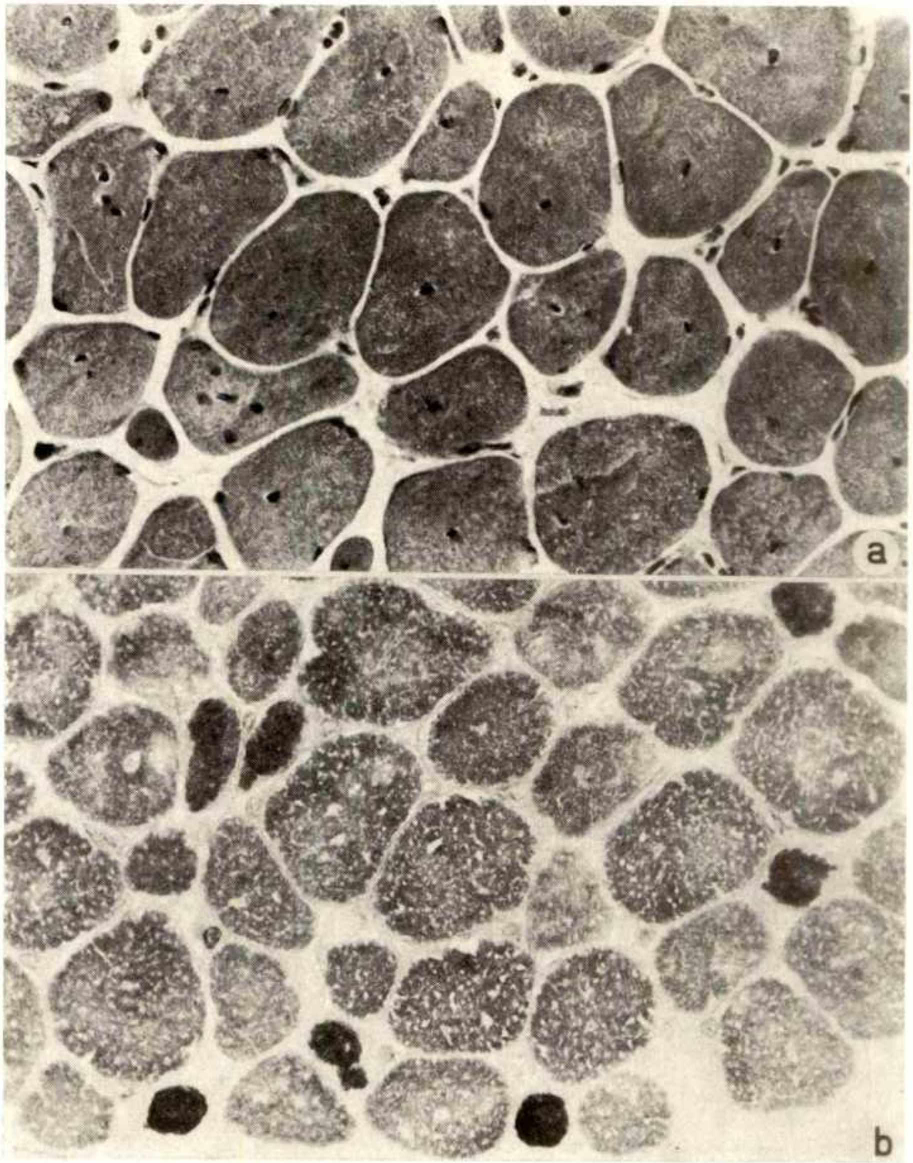

FIG. 4 *Muscle biopsy of Case 1 (right anterior tibial muscle). a) Variation in fibre diameter and centralization of the nuclei in most fibres. (Cryostat section: H and E. × 330.) b) Type II fibres (darkly stained) are less numerous and atrophied. (Cryostat section, myofibrillar ATPase* p*H 9·4. × 330.)*

second case. Campbell, Rebeiz, and Walton (1969) described perinuclear myofibrillar degeneration, but this was not found by other authors.

The clinical and histological findings of our two patients correspond to the published descriptions of centronuclear myopathy. However, in most patients, histochemical studies show a normal distribution of type I and II fibres. Atrophy of type I fibres was clearly found in 6 cases (Badurska *et al.*, 1969; Bethlem *et al.*, 1969, 1970; Engel, Gold, and Karpati, 1968; Karpati, Carpenter, and Nelson, 1970). In our 2 cases we found an obvious numeral predominance of type I fibres. The atrophy was usually of type II fibres in the first case, and type I fibres in the second case. A special feature in our patients was the absence of the anterior arch of the atlas vertebra, which has not been described until now.

The familial occurrence of the disease was noted by several authors. Though different modes of inheritance have been proposed, insufficient data are available for definite conclusions to be drawn.

The clinical, radiological, electrocardiographic, and necropsy findings in the first patient clearly indicate the presence of 'cardiomyopathy', with diffuse cardiac dilatation, extensive fibrosis, and compensatory focal hypertrophy of the myocardium. In the second patient slight congenital aortic stenosis was present. This diagnosis was based on the clinical findings and the character of the carotid pulse recording. Nevertheless, it is reasonable to suspect that this patient also presented some degree of 'cardiomyopathy'. Indeed, the cardiac enlargement at the age of 14 was out of proportion to the degree of the aortic stenosis. Further, extreme left axis deviation without other signs of left ventricular hypertrophy was the main electrocardiographic abnormality in both brothers. This electrocardiographic pattern suggests intraventricular conduction disturbance of the left anterior hemiblock type.

Although the association of peripheral muscle disease such as progressive muscular dystrophy and 'cardiomyopathy' is well known, until now this association has received only slight attention in centronuclear myopathy.

Bethlem *et al.* (1969) described a 16-year-old girl with centronuclear myopathy and heart failure, attributed to a 'cardiomyopathy' of unknown origin. No further data were given. In 2 other patients, right ventricular hypertrophy was mentioned (Bradley, Price, and Watanabe, 1970; Brooke and Williamson, 1969). Though not discussed by the authors, this could have been secondary to ventilatory dysfunction caused by chronic respiratory muscle weakness and not to 'cardiomyopathy'. In a study on skeletal muscle in idiopathic cardiomyopathy, Shafiq *et al.* (1972) described one case (No. 11) with type I fibres which were hypotrophic but more numerous than normal (type I fibre predominance). Though not mentioned in the description by these authors, numerous internal nuclei are visible in the illustrated figure of this case, which possibly could be considered as a 'cardiomyopathy' associated with a centronuclear myopathy.

The present two cases and the cases of Bethlem *et al.* (1969) and Shafiq *et al.* (1972) clearly indicate that centronuclear myopathy may be associated with 'cardiomyopathy', which can cause death at an early age. This implies that centronuclear myopathy cannot always be considered as a benign disease.

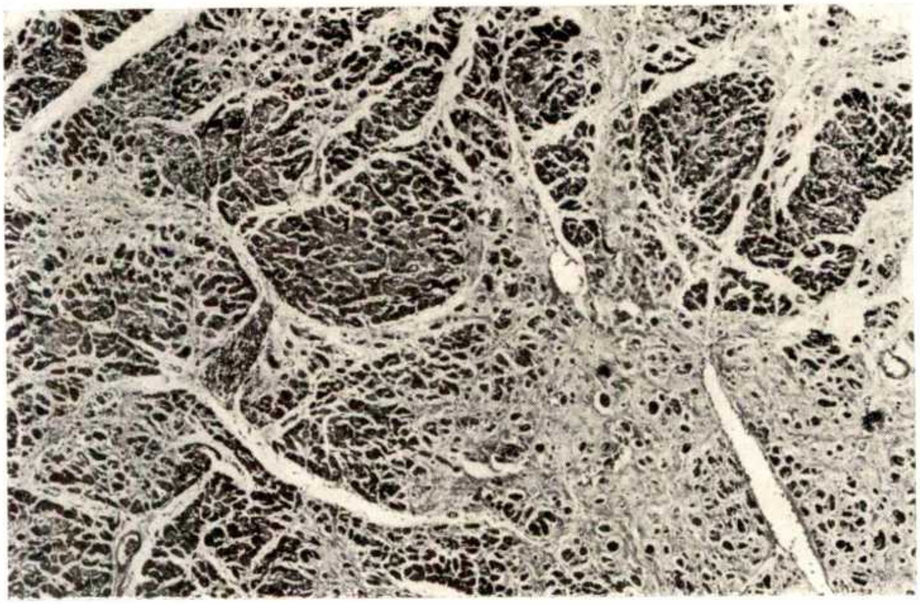

FIG. 5 *Case 1 : Extensive fibrosis and focal hypertrophic fibres are present in the myocardium (fixation about 10 hours after death, Masson trichrome. × 50).*

Cardiological examination to look for the possible presence of cardiac involvement seems mandatory in all cases of centronuclear myopathy.

We are indebted to Dr. V. W. Armbrustmacher, Dr. K. M. Earle, and Dr. A. McAllister, Jr (Armed Forces Institute of Pathology, Washington, D.C.) and Dr. W. K. Engel (National Institute of Health, Bethesda) for their advice.

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Anomalous iliac compliance in children with a single umbilical artery

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Arterial compliance (C) has been measured in 18 children known to have had a single umbilical artery at birth. Non-invasive ultrasonic Doppler techniques were used to measure C for the aorta, iliac, and leg arteries. Anomalous compliance was found between the two iliac vessels, and it is suggested that this is the result of haemodynamic stress-induced changes during development. The demonstration that the form of large arteries may be changed by altered haemodynamic stress and that their physiological function is thus affected, may have important implications in the pathogenesis of degenerative disease.

In many organs and tissues, interference with growth at critical periods may affect their ultimate structure and function. Events of this type have been documented for the central nervous system (see Dobbing, 1974 for review), for the immunoreactive tissues (Smythe *et al.*, 1971; Mathews *et al.*, 1972) and the skeleton (Stewart *et al.*, 1972), and for the fat organ (Brook, 1972). No such record has been made for the large arteries.

The elastic behaviour of the arterial wall at physiological pressures is almost entirely determined by the structure of the tunica media (Wolinsky and Glagov, 1964). Changes in the form of the media of large elastic arteries occur rapidly when the tension in the wall of the vessel is increased (Berry, 1969), and in the aorta chemical changes, notably a rapid increase in elastin content, occur soon after birth (Berry, Looker, and Germain, 1972). Certain aspects of aortic elastic function are known to change with age—for example, volume distensibility changes considerably in the first two decades of life (Gosling and King, 1975).

It is possible that changes in flow and pressure in large arteries during development affect the form of the media, and hence its functional characteristics. The studies of Bryan and Kohler (1974) on a large population of children identified (by examination of the umbilical cord) a number with unilateral absence of an umbilical artery. In these individuals the pattern of blood flow in the iliac vessels would be altered in intrauterine life. The study presented here was undertaken in order to explore the extent to which such departures from normal haemodynamic load might affect the medial structure in the iliac pathways.

It has only recently become practicable to measure vessel compliance *in vivo* by a non-invasive method using ultrasound, where the simultaneous use of two ultrasonic Doppler-shift blood velocimeters permits definition of a specific arterial pathway and allows determinations of compliance (Gosling and King, 1974). This method has been applied here.

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Subjects and methods

Vessel compliance may be defined as $C = (\Delta D/D)/\Delta P$ ....(1), when D is the lumen diameter at perfusion pressure P, and ΔD is the increase in diameter of the lumen produed by an increment ΔP in pressure. If we express the value of C as 'per cent per 10 mmHg (13·3 kPa) pressure increment', this intrinsic wall property may be compared in subjects with differing pulse pressures.

Over a given vessel length, L, it is the average compliance of the vessel pathway that causes the delay or transit-time (T) found between corresponding points of the proximal and distal pulse waves (of flow and/or pressure) observed for the same heart beat. The positions of the Doppler probes define the length of vessel pathway to be assessed (L). C is given by:

$$C \text{ per cent per 10 mmHg (13·3 kPa)} = 0{\cdot}667 \left(\frac{T}{L}\right)^2 \quad ..(2)$$

taking average density of whole blood as 1·00, T in milliseconds and L in centimetres.

Eighteen children born with a single umbilical artery aged between 5 and 9 years were examined. Controls in this age range were taken from a study by Gosling and Laogun (1976) on the variation of arterial compliance with age in normal children. Each subject, controls and those with single umbilical artery, were rested, supine and horizontal, for at least 10 minutes before the examination began.

Data collection

Two 5 MHz ultrasonic Doppler-shift blood velocimeters (Parks 701) were used in conjunction with a Sony stereo-tape recorder.

Measurement of transit-time

With subject supine and horizontal, Doppler detectors were placed on the skin successively in pairs over:

a) Left subclavian artery in the supraclavicular fossa and abdominal aorta just proximal to the aortic iliac bifurcation, i.e. over the aorta 0·1 to 0·2 m proximal to a line joining the iliac crests (aortic segment).
b) Aortic bifurcation (as defined above) and the left and right common femoral arteries in turn at the inguinal ligament (iliac segments).
c) Left common femoral site as above and the left posterior tibial artery (leg).

Probes were pointed towards the heart in all cases.

Pressure

Occlusion cuff pressures were taken in the right arm, the distal brachial artery being monitored with both stethoscope and Doppler detector independently.

Data processing

The Doppler-shift signals from the two detectors were recorded (at the sites above) and later analysed by a continuous two channel Spectrascribe (Coghlan, Taylor, and King, 1974). The sonagram traces of signals from the distal site are delayed compared with those from the proximal site, and this transit-time T is measured from 'foot' to 'foot' of the sonagram waveforms (see Fig. 1). The resolution is limited by the ease of recognition of the foot. Using 5 MHz carrier wave we can usually achieve a value correct to ±4 ms. Since perfusion pressure is respiration modulated, small changes in T are found for successive heart beats. Thus observations were always made over several respiration cycles—usually 30 to 40 consecutive heart beats.

Arterial pathway length

The segment L was in all cases a surface approximation. For site a) above, length was measured from the anterior midpoint of the sternal end of the clavicle to the position of the detector on the abdomen. For sites b) and c) distance was measured between detectors.

Results

Subjects

Table 1A shows age, sex, height, weight, blood pressure (BP), mean arterial pressure (P), and pulse pressure (P) of the 18 cases with single umbilical artery measured in this study. Table 1B

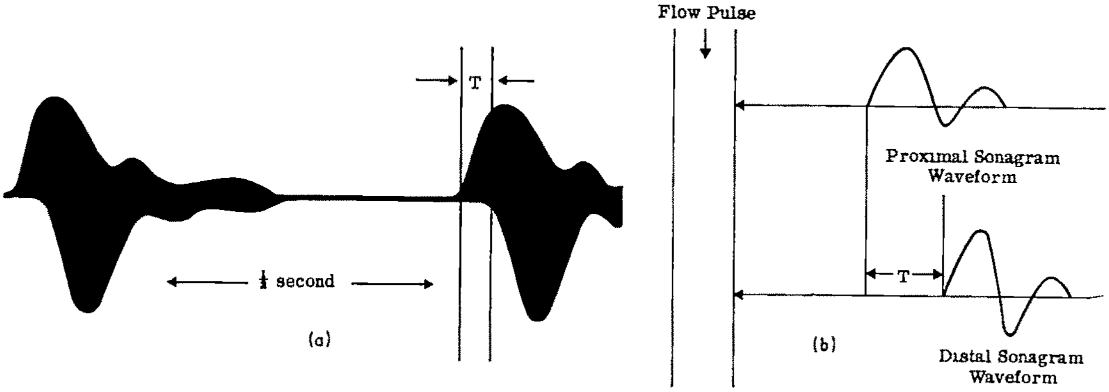

FIG. 1 *Spectrascribe two-channel display of Doppler-signals from abdominal aorta and common femoral. Doppler frequency (proportional to red-cell velocity) 0 to 5 kHz on y axis, time on x axis with blackness of trace proportional to number of red cells moving at any given velocity. Inverting distal trace allows easy and accurate measurement of foot to foot transit time, T, for any number of successive heart beats. Note well-defined maximum frequency outline or waveform of each sonagram. b) The foot-to-foot delay time T between two sonagram waveforms measured simultaneously at different points known distance apart on blood vessel allows* in vivo *estimation of vessel compliance.*

TABLE 1A

Case No.	*Age (yr mth)*	*Sex*	*Weight (kg)*	*Height (m)*	*BP (mmHg)*	P	*ΔP*
1	7 3	F	23·36	1·21	108·85	93	23
2	8 3	F	25·09	1·27	98/58	81	40
3	5 10	M	16·98	1·18	98/64	75	34
4	6 6	F	19·73	1·13	96/54	68	42
5	6 2	F	18·37	1·16	104/58	73	46
6	5 6	M	23·33	1·15	88/58	68	30
7	7	F	23·13	1·15	102/70	81	32
8	8	F	25 4	1·30	97/55	69	42
9	6 10	F	22·45	1·23	98/55	69	43
10	8 2	F	21·32	1·19	92/54	67	38
11	8 4	F	23·59	1·26	90/56	71	44
12	6 6	F	23·99	1·18	93/50	72	43
13	5	F	18·37	1·09	102/55	71	47
14	6 8	F	38·1	1·32	118/58	78	59
15	7 2	F	22·68	1·19	101/58	72	43
16	6 5	M	23·33	1·23	96/56	69	40
17	6 5	F	21·32	1·13	101·58	72	43
18	5	M	17·69	1·05	108·52	71	56

Conversion from Traditional Units to SI Units: 1 mmHg≈0·133 kPa.
P Mean pressure. ΔP Pulse pressure.

TABLE 1B

No. of normal children	*Age range (yr)*	*Average weight (kg)*	*Average height (m)*	*Average BP (mmHg)*	*Average* P	*Average ΔP*
12	5–6	20·19	1·14	89/56	67	33
25	6–7	22·54	1·19	97/58	71	39
16	7–8	25·91	1·28	101/59	73	42
19	8–9	27·16	1·32	101/60	74	41

Conversion from Traditional Units to SI Units: 1 mmHg≈0·133 kPa.
P Mean pressure.
ΔP Pulse pressure.

shows the same values for normal children in the same age range as those with single umbilical artery.

Compliance in normals: aortic, iliac, and leg segments

The values of mean compliance C with standard deviation found in the number of normal individuals shown in Table 1B for the various defined arterial pathways are set out in Table 2.

TABLE 2

Age (yr)	*5 to 6*	*6 to 7*	*7 to 8*	*8 to 9*
No. of normal children	12	25	16	19
C±SD				
Aorta	2·30	2·36	2·50	2·67
	±0·19	±0·18	±0·20	±0·16
Left iliac	2 03	2·07	2·11	2·14
	±0·20	±0·20	±0 20	±0·21
Right iliac	1·97	1·97	2·12	2·10
	±0·17	±0 21	±0·21	±0·18
Leg	1·34	1·27	1·14	1·08
	±0·16	±0·18	±0·16	±0·21

Reproducibility of compliance values

In October 1974 recordings were taken of Doppler-shift signals and pathway lengths for the sites a), b), and c), as described in the method section, from the 18 subjects with single umbilical artery. Ten of these subjects were then re-examined in January 1975. Fig. 2 compares the values of compliance found on these two occasions for the aorta right, and left iliac pathways.

Compliance in cases with single umbilical artery: aorta, iliacs, and leg

Fig. 3 shows the values of mean compliance as $\bar{C}$ per cent per 10 mmHg (13·3 kPa), with standard deviation, and number of time delay (T) observations, N, for the aorta and left and right iliacs. The

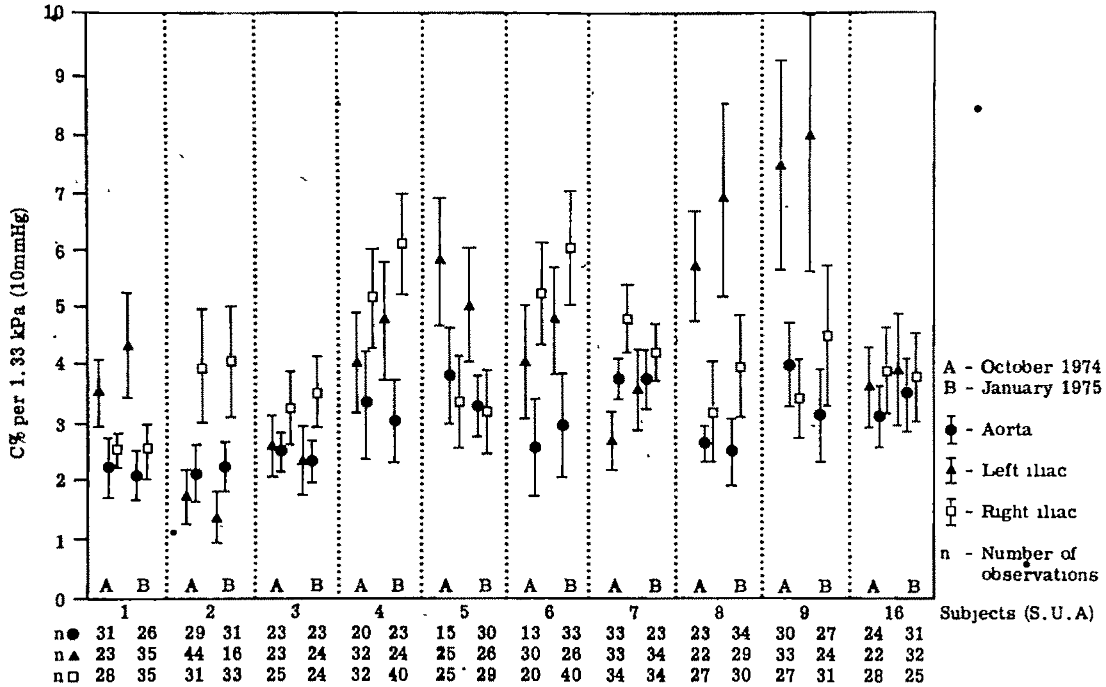

FIG. 2 *Arterial compliance values for aorta, left, and right iliacs, of subjects with a single umbilical artery (S.U.A.) measured on two occasions about four months apart. Agreement of values shows reproducibility of method.*

values are averaged measurements for the 10 subjects examined on visits A and B (shown in Fig. 2) and those of the remaining 8 subjects are calculated from readings taken at the first examination.

In all of the cases examined one iliac pathway was found to be more compliant than the other (left>right for 9 subjects and right>left for 9 subjects). In Cases 1 to 15 this difference was statistically significant at better than the 99·9 per cent confidence level. In Cases 16 and 17, though the right iliac artery was more compliant than the left, the confidence level in these findings was low, e.g. Case 16: $0{\cdot}02<P<0{\cdot}05$, Case 17: $0{\cdot}2<P<0{\cdot}3$. However, in Case 16 the right iliac was significantly more compliant than the aorta ($P<0{\cdot}001$), and in Case 17 both iliacs were more compliant than the aorta at this level.

In 12 cases the most compliant iliac pathway was significantly more compliant than the aorta and in 5 cases *both* iliacs were more compliant than the aorta ($P<0{\cdot}001$). Only in Case 18 were iliac pathway compliance values *not* significantly higher than that of the aorta (L.I. $0{\cdot}3<P<0{\cdot}4$, R.I. $0{\cdot}1<P<0{\cdot}2$), though the right iliac was more compliant than the left with $0{\cdot}001<P<0{\cdot}01$.

Leg arteries showed no significant deviations between right or left or from normal values.

Discussion

A missing umbilical artery is associated with an increase in incidence of major malformation, prematurity and smallness for dates. This has been illustrated by Bryan and Kohler (1974) who found, in a survey of 20 000 placentas, 143 with one artery instead of two. Of these 143 infants, 25 had major malformations, 20 being stillborn or dying in the first week of life; 33 were of low weight and 24 were preterm. It is from the group with no apparent malformations that the 18 children in this study were taken.

Follow-up studies on these children are in progress and have been reported elsewhere (Bryan and Kohler, 1974). In summary, there appears to be no readily observable characteristic that separates them from the general population. In particular, there is no evidence of leg shortening on either side, confirming the findings of Johnsonbaugh in 1973. In 8 infants known to have single umbilical artery who were examined in early life (up to 15 months), Johnsonbaugh commented that the results of transumbilical aortography in 5 infants showed the 'incidental finding of a markedly reduced caliber of common and of internal iliac arteries on the side where the umbilical artery was absent'.

Meyer and Lind (1974) have examined histologically the vessels of 8 infants with single umbilical artery between 2½ days and 4 years of age. They found that the common iliac artery on the side of the missing umbilical artery was small and muscular while that on the opposite side was enlarged, elastic in type, and showed pronounced calcification. Established atherosclerotic changes were also found in children of 18 months and 4 years of age.

In our study there is a striking increase in compliance in one iliac artery, which we have not found in controls. The aortic segment shows consistently higher compliance values than normals when means are compared. However, leg artery compliances do not differ significantly in the two groups. We suggest that haemodynamic stresses are responsible for all these findings, particularly those present on the side where the umbilical artery had existed in fetal life, and we suggest the following simple model; assume flow of blood to remain the same between fetus and placenta in normal subjects and those with single umbilical artery. The iliac artery from which the umbilical artery originates is now required to accommodate twice the volume flow. Since the flow is pulsatile this could be accomplished by doubling the volume strain $\Delta V/V$, i.e. doubling the compliance. From Fig. 3 it may be seen that in single umbilical artery (Cases 1 to 15) the most compliant iliac pathway has a compliance greater than the aorta by an average factor of 1·9, whereas normal iliac compliance is found to be about the same or slightly less than the aorta (see above).

Persisting with this model, it may be shown that the compliance as defined in eq. 1 may be given by

$$C = (3/8) \cdot (1/E)\,(D/h)$$

where E is the incremental modulus of the arterial wall, D the average lumen diameter, and h the wall thickness (Newman, Gosling, and Bowden, 1971). Thus we see that if the intrinsic elastic material of the artery wall does not change, i.e. E remains the same, then observed results can be explained by doubling D/h. Recent studies (Berry, Greenwald,

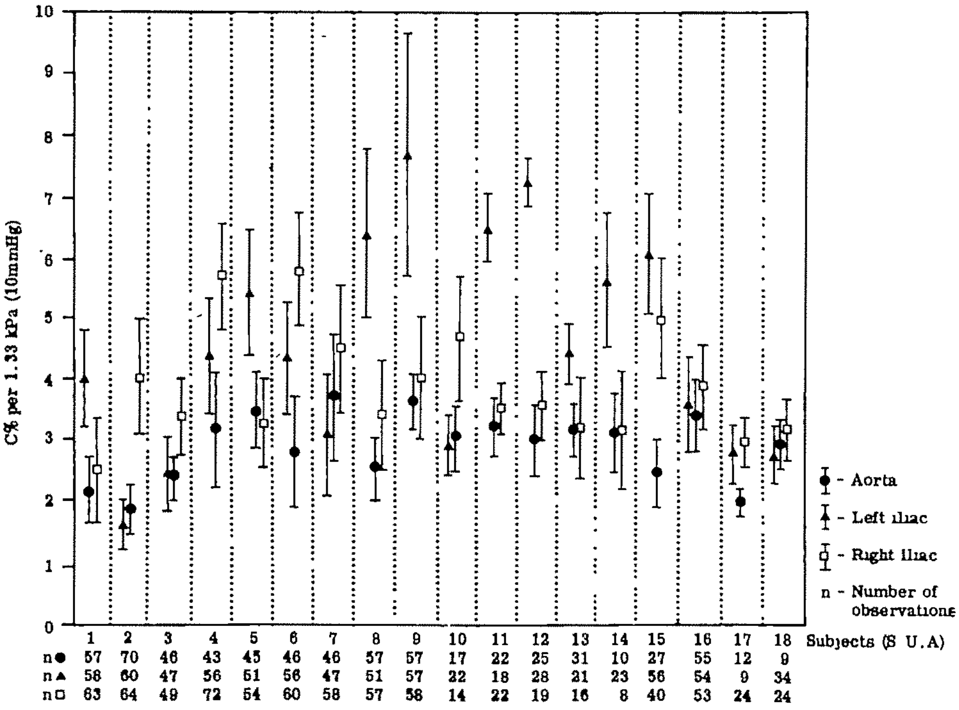

FIG. 3 *Comparison of compliance of aortic and iliac pathways in 18 subjects with single umbilical artery (S.U.A.).*

and Rivett, 1975) have shown that in the rat E does not change as vessels grow and develop. It has also been suggested (Gosling and King, 1975) that in health changes in E and D/h invoked by normal physiology are such as to tend to minimize changes in compliance C, and that one of the first steps in arterial disease is a significant departure of C from 'in health values'.

We, therefore, conclude that the results presented here are consistent with the model suggested, i.e. that abnormal haemodynamic loading of the iliac pathway *in utero* is sufficient to change the value of C for the iliac pathway and to some extent the aorta. It is likely that the value of D/h alters to produce most of the change with inevitable structural rearrangements of the media. This conclusion is supported by the findings of Meyer and Lind.

The demonstration that the form of large arteries may be changed by altered haemodynamic stress and that their physiological function is thus affected, may have important implications in the pathogenesis of degenerative disease.

Large elastic arteries continue to develop for the first two decades of life. Haemodynamic stresses may vary between individuals during this time; as Beresford and Holland (1973) have shown, children have blood pressure levels that relate to the levels of their parents by the age of 6 years. If such variability produces subtle arterial changes these may, in part, be responsible for variations in susceptibility to degenerative arterial disease.

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Prognostic value of the electrocardiogram in endocardial fibroelastosis

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Nine children with endocardial fibroelastosis were followed from the time of admission with congestive heart failure until either death or discharge. Review of multiple clinical features showed that only the electrocardiographic pattern could be correlated with death or survival. The presence of a delayed transition zone with anterior force loss on the initial electrocardiogram ('infarct pattern') was noted in all the children who died. Progression of these changes with a pattern of anterolateral 'infarct' in two and inferior wall 'infarct' in two occurred before death. Necropsy on three of the four children confirmed the diagnosis of endocardial fibroelastosis. There was extensive fibrosis and thinning of the left ventricular myocardium as well as involvement of the mitral valve structures. Review of published cases supports the view that an 'infarct' pattern in a child with endocardial fibroelastosis is usually associated with death and that this pattern is a negative prognostic sign for survival.

Primary endocardial fibroelastosis (EFE) usually occurs in infants under 1 year of age and presents with congestive heart failure (Manning and Keith, 1964; Forfar *et al.*, 1964). There is thickening of the endothelial layer of the left ventricle, often with extension on to the papillary muscles, chordae, and mitral valve leaflets. The left atrium may also be involved while the right side is less frequently affected. Mitral regurgitant murmurs, resulting either from dilatation of the left ventricle or from involvement of mitral valve structures, are common (Moller *et al.*, 1964). Secondary EFE is often associated with congenital heart lesions, especially left heart obstruction or underdevelopment (McCormick, 1958; Sellers, Keith, and Manning, 1964). It may also be seen in acquired heart disease but is usually patchy in its distribution.

EFE occurs in dilated and constricted forms (Moller *et al.*, 1964; Lambert and Vlad, 1958). The former is the more common primary type seen in infants; the latter is seen more frequently in adults where the left ventricular chamber is normal in size but the ventricular wall is greatly thickened (Van Buchem, Arends, and Schröder, 1959). Whether EFE in these two forms is a single entity remains uncertain; EFE is now frequently regarded as a form of endomyocardial fibrosis, which may have a number of aetiologies (Apley, 1961; Hastreiter and Miller, 1964).

EFE in children has usually been a diagnosis of exclusion; only occasional biopsies have been done during life, and commonly the diagnosis is only confirmed at necropsy (Manning and Keith, 1964; Forfar *et al.*, 1964; Moller *et al.*, 1964; Hastreiter and Miller, 1964). However, a significant percentage of children with this diagnosis do recover and apparently return to normal cardiac function. In nine children with EFE, seen at the Johns Hopkins Hospital, the presenting electrocardiogram and its subsequent changes seemed to correlate best with the eventual outcome. A full evaluation was undertaken in these nine children, with follow-up until death in four, discharge from clinic in four, and loss to follow-up in one.

Clinical material

Nine children, eight Negro and one Caucasian, three male and six female, were followed from 1964 to 1972, when the children were either dead or discharged from follow-up.

The nine patients were initially admitted to the hospital when they were aged 3 to 10 months, with

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TABLE 1 *Clinical features on admission*

Case No., race, sex, age	*Physical examination*	*X-ray*	*Hb (g/dl)*	*Viral studies*	*Rubella titre*	*Mumps skin test*	*Catheterization data*
1, N, M, 8 mth	CHF, PA, quiet HS, 2/6 MR murmur	CTR=72%; LLL atelectasis	9·9	Neg.	Neg.	Neg.	RH pressures, coronaries normal; PA; high LVED
2, N, F, 5 mth	CHF, PA, quiet HS, no murmur	CTR=73%; LLL atelectasis, ?RLL	10·0	Neg.	Pos.	Neg.	RH pressures, coronaries normal; LV not entered
3, C, F, 6 mth	CHF, quiet HS; no murmur	CTR=67%; LLL pneumonia	9·7	Not done	Not done	Not done	Not done
4, N, F, 5 mth	CHF, quiet HS; no murmur	CTR=67%; LLL pneumonia	9·4	Neg.	Pos.	±	RH pressures, coronaries normal; high LVED; mild MR
5, N, F, 9 mth	CHF, PA, quiet HS; 2/6 MR murmur	CTR=70%; LLL pneumonia	10·4	Neg.	Neg.	Neg.	RH pressures, coronaries normal; PA; LV not entered
6, N, F, 4 mth	CHF, PA, quiet HS; 3/6 MR murmur	CTR=73%; LLL pneumonia	9·4	Neg.	Neg.	Not done	Mild increase RH pressures; normal coronaries; high LVED; mild MR
7, N, M, 10 mth	CHF, PA, quiet HS; no murmur	CTR=71%; LLL atelectasis	8·8	Pos.	Neg.	Neg.	Moderate increase RH pressures; PA; normal coronaries; high LVED; mild MR
8, N, F, 6 mth	CHF, quiet HS; 2/6 MR murmur	CTR=67%; LLL atelectasis; RLL pneumonia	11·4	Not done	Not done	Neg.	Severe increase RH pressures; normal coronaries: high LVED; mild MR
9, N, F, 3 mth	CHF, quiet HS; no murmur	CTR=72%; LLL atelectasis	9·8	Neg.	Not done	Neg.	Not done

N, Negro; C, Caucasian; CHF, congestive heart failure; CTR, cardiothoracic ratio; HS, heart sounds; LLL, left lower lobe; LVED, left ventricular end-diastolic pressure; mth, months; MR, mitral regurgitation; PA, pulsus alternans; RLL, right lower lobe; RH, right heart; ±, equivocal.

the diagnosis of congestive heart failure and either left lower lobe atelectasis (5) or left lower lobe pneumonia (4); two also had right lower lobe opacities (Table 1). On physical examination, all were in congestive failure with quiet heart sounds; four had pulsus alternans and four had murmurs of mitral regurgitation. All were anaemic (Hb 8·8–11·4 g/dl). All had increased cardiothoracic ratios (67–73%), as a result of left ventricular and left atrial enlargement, and pulmonary venous engorgement. Viral studies[1] were negative in six, and a rise in Coxsackie titres were observed in one. Rubella antibody titres were done in six and were positive in two. Mumps skin test was done in seven, with negative results in six and an equivocal response in one. Cardiac catheterization in seven children showed normal coronary arteries in all, and no associated congenital defect. Four had normal right heart pressures, while in the remaining three these pressures were raised in varying degree. Pulsus alternans was present in four. The left ventricle was entered in five of the seven and the end-diastolic pressure was high in all. Of the four who had left ventricular cineangiography, all showed mild mitral regurgitation, with a dilated and poorly contracting left ventricle.

Preadmission history is shown in Table 2. Eight children were born at full term, with normal birthweights, and one was delivered prematurely with a birthweight of 1558 g. Sibling rank varied from first to eighth, with maternal age from 17 to 30 years. Four mothers had had mumps in childhood, two had not, and three were uncertain. Prenatal complications were absent in four; premature rupture of membranes, with premature delivery occurred in one mother; mild toxaemia was present in four, and exposure to rubella in the first trimester occurred in one. Family history was negative in four. Two mothers had had previous early miscarriages and one of these had had two previous premature infants as well. Three mothers had asthma but were not on continuous therapy at the time of pregnancy. One mother had sickle trait and epilepsy, for which she was treated with phenytoin. Family history of heart disease was limited to rheumatic heart disease in one father and unknown heart disease causing death at age 16 in another paternal aunt.

After discharge, all children were followed in the outpatient department (Table 3). All responded initially to treatment with digoxin and 3 subsequently continued to do well with a decrease in heart size on *x*-ray and no recurrence of heart failure or respiratory infections. One of these three was restudied at age 4 years with normal catheterization results. All three were taken off digoxin at

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[1] Acute and convalescent sera for antibody titres for Coxsackie A and B, Echo, and in some cases other viruses, and nasopharyngeal and stool cultures for viral isolation.

TABLE 2 *Pre-admission history*

Case No.	*Birth weight (g)*	*Maternal age (y)*	*Sibling rank*	*History of mumps in mother*	*Prenatal complications*	*Family history*
1	3345	21	1	Unknown	Mild toxaemia	Negative
2	2380	17	1	Yes	None	Sickle trait and epilepsy in mother; RHD in father
3	3684	24	3	Yes	Rubella exposure in 1st trimester; mild toxaemia	Asthma in mother; one previous miscarriage
4	2749	17	2	No	None	Asthma in mother
5	2976	26	2	Yes	None	Negative
6	3032	21	2	No	Mild toxaemia	Asthma in mother
7	4167	30	8	Unknown	Excess weight gain: on iron and 'diet pills'	Negative
8	1558	25	4	Unknown	Premature rupture of membranes	3 of 4 children premature; one miscarriage; paternal aunt died at age 16 from unknown heart disease
9	2268	26	3	Yes	None	Negative

RHD, rheumatic heart disease.

TABLE 3 *Course of illness*

Case No.	*Clinical course*	*X-ray*	*Age at death*	*Discharge*	*Repeat catheterization*
1	Continued CHF with recurrent infections; MR, increasing	CTR from 72 to 82%; recurrent LLL atelectasis	17 mth	—	No
2	Recurrent infections with FTT for one year; then improved; no murmur	Lungs clear: CTR from 73 to 55%	—	Off digoxin at 3 years; discharged at 5 years	Yes: normal study at 4 years
3	No further problems; no murmur	Lungs clear; CTR from 67 to 51%	—	Off digoxin at 3½ years; discharged at 5 years	No
4	Recurrent infections, persistent anaemia; FTT; borderline CHF; no murmur	Lungs clear; CTR same at 67%	16 mth	—	No
5	No further problems; no murmur	Lungs clear; CTR from 70 to 60%	—	Off digoxin at 3 years; left clinic	No
6	No further problems; no murmur	Lungs clear; CTR from 73 to 58%	—	Off digoxin at 3 years; discharged at 5 years	Yes: normal study at 4 years
7	Continued CHF, recurrent infections; MR murmur	Persistent LLL atelectasis; CTR same at 71%	30 mth	—	Yes: 18 mth-impaired LV function with high LVED; MR (phenolization at 2 years)
8	Continued CHF, recurrent infections; intermittent MR	Persistent LLL atelectasis; CTR from 67 to 70%	36 mth	—	No
9	Recurrent infections with CHF for 1 year; then improved; no murmur	Lungs clear; CTR from 72 to 60%	—	Off digoxin at 5 years; discharged at 8 years	Yes: normal study at 5 years

CHF, congestive heart failure; CTR, cardiothoracic ratio; FTT, failure to thrive; LLL, left lower lobe; LV, left ventricle; LVED, left ventricular end-diastolic pressure; MR, mitral regurgitation.

3 years of age. Two were discharged from clinic attendance at 5 years of age; the third was lost to follow-up at 3 years of age, clinically doing well. Six children, after initial improvement, continued to have recurrent infections with 'failure to thrive' and chronic congestive failure. Four of these died between the ages of 16 and 36 months. The other two children did poorly for about seven to twelve months but then improved. Digoxin was stopped at ages 3 and 5 years. Catheterization was performed at ages 4 and 5 years with normal results, except for possible slight impairment of left ventricular function in one. These two children continued to do well and were discharged from clinic at 5 and 8 years of age.

The four children who died all continued to have recurrent episodes of atelectasis, pneumonia, and heart failure. The anaemia persisted or worsened in spite of treatment; the cardiothoracic ratio initially showed no improvement and then increased. Two children developed a chronic left lower lobe atelectasis, and one of these collapsed the entire left lung during his terminal admission; these two died while in hospital and necropsy confirmed the diagnosis of EFE. The other two children died at home at 17 and 32 months of age. There was no necropsy on the former. The latter had had a phenolization done at 2 years of age, with minimal clinical change; necropsy on this infant also confirmed the diagnosis of EFE.

Various clinical features were examined for their prognostic value. All children were treated the same way with digoxin and diuretics initially. The digoxin was increased with growth until the age of 2 to 4 years in the five children who survived. The past history and the admission history were not remarkably different. Physical examination was not useful since all were in failure; pulsus alternans and mitral regurgitation were present in those survived and in those who died. Left lower lobe atelectasis with or without penumonia was present in all and cleared in all initially. All responded to treatment and were discharged; three maintained their improvement; two had continuing problems for seven and twelve months before manifesting further improvement; four continued with problems with no major periods of improvement up to the time of their deaths. The decrease in cardiothoracic ratio was slow, with even the 'normals' staying above 60 per cent for months and years. At 5 years of age, two children had a ratio of 51 and 58 per cent;

TABLE 4 *Electrocardiographic features*

Case No.	*Electrocardiogram on admission*	*Change in electrocardiogram*	*Result*
1	LVH; axis+120°; transition at V5; ST elevation in anterior leads; T waves inverted over left praecordium	Massive 'infarct' pattern with QS in V1-6; ST elevation in anterior leads	Died: PM showed marked fibrosis of LV with multiple thrombi; confirmed EFE
2	LVH; axis+20°; transition at V2; ST elevation V1-3; depressed V4-6; T wave inverted in left leads	Decrease in voltage; transition never delayed; ST return to normal; T wave normalization but some flattening	Alive and well; normal study at 4 years of age; no medications
3	LVH; axis+50°; transition at V3; no ST changes; T wave inverted in left leads	Decrease in LV voltage; normal ECG with upright T waves	Alive and well; no medications
4	LVH; axis+60°; transition at V5; ST elevation V1-3; T wave inverted in left leads	Persistent LVH and T inversion; transition always delayed	Died; no PM
5	LVH; axis+40°; transition at V2; no ST changes; T wave inverted in left leads	Still had LVH at time lost to follow-up; improved T waves	Lost to follow-up; off digoxin and clinically well
6	LVH; axis+60°; transition at V2; ST elevation V1-3; T wave inverted in left leads	Complete normalization	Alive and well; normal study at 4 years of age; no medications
7	LVH; axis+20°; transition at V6; no ST changes; T wave inverted in left leads	Progressive loss of left, anterior, inferior forces; LAD -65°; T wave changes	Died 4 months after phenolization, age 30 months; necropsy showed EFE, fibrosis++
8	LVH; axis+40°; transition at V4; no ST changes; T wave inverted in left leads	Loss of inferior forces with LAD -30°; increasing ST, T wave changes; transition to V5-6	Died at 3 years; PM showed EFE with fibrosis and thinning++
9	LVH; axis+20°; transition at V3; no ST changes; T wave inverted in left leads	Borderline LVH; transition at V2 with normal S-T, T waves	Alive and well; normal study at 5 years of age; on no medications

EFE, endocardial fibroelastosis; LVH, left ventricular hypertrophy; LV, left ventricle; LAD, left axis deviation.

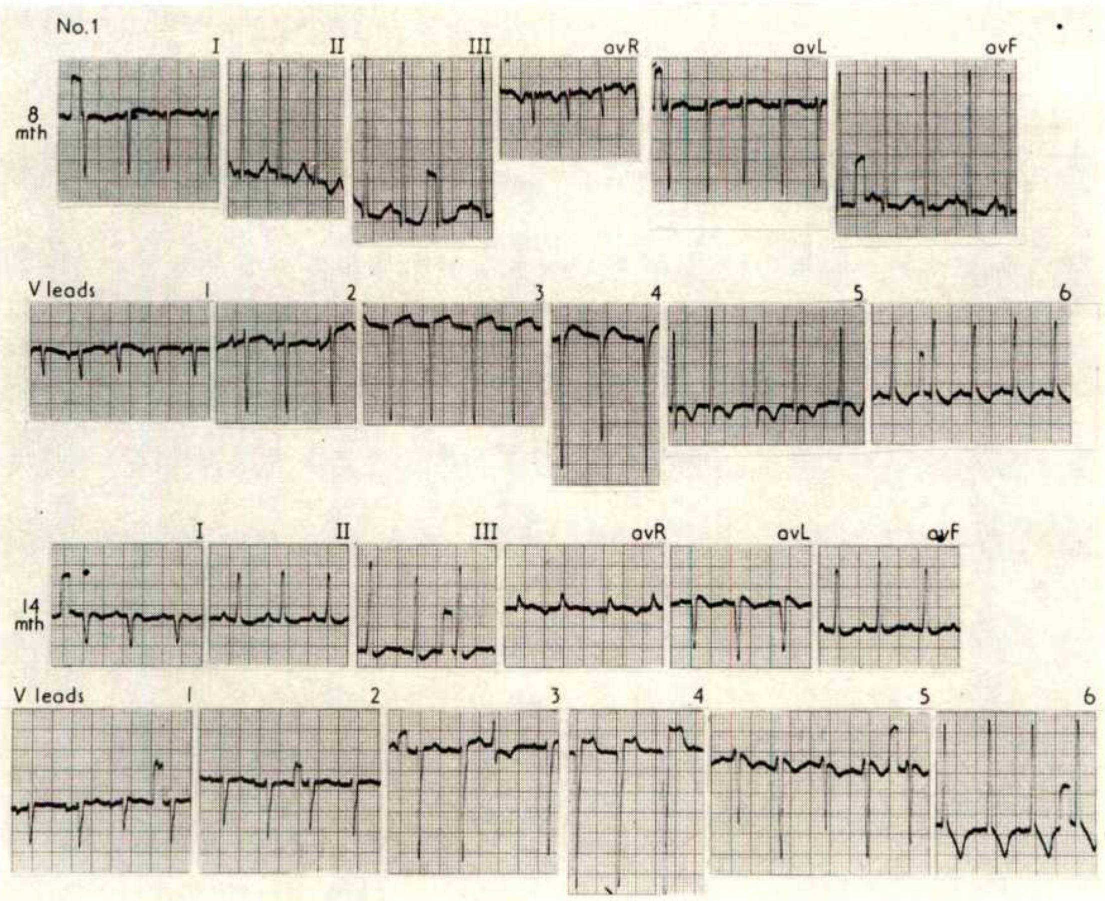

FIG. 1 *The admitting electrocardiogram at 8 months of age and an electrocardiogram at 14 months, 2 months before death, for Case 1. Note the delayed transition in both, V4-5 at 8 months and V5-6 at 14 months. ST segment elevations are present in the mid-praecordial leads and T wave inversion has increased in V6. Loss of anterior force was confirmed on vectorcardiogram with early posterior displacement of the outgoing limb on the transverse plane.*

at 8 years of age, one child had a ratio of 60 per cent. After treatment of heart failure, cardiac catheterization was performed but showed no differences between the children who subsequently did well and those who died.

Evaluation of electrocardiograms

The admission electrocardiogram (Table 4) in all nine children showed left ventricular hypertrophy, with inversion of the T waves in the left praecordial leads. ST segment changes were variable or absent. Mean QRS axis ranged from +20° to +120°. Three children had obvious loss of anterior force with a delayed transition zone (two in V5, one in V6); this was confirmed by vectorcardiography in two, with early posterior displacement of the outgoing limb in the transverse plane with a resultant clockwise loop. Two children had suggestive loss of anterior force, with a transition in V4 in one and V2 in the other. Vectorcardiograms on these showed an early posterior displacement only in the first.

In the five children who survived, the electrocardiogram never showed a loss of myocardial forces initially or during the subsequent hospital course and follow-up in the outpatient clinic. Though regression of the left ventricular hypertrophy pattern was often slow, there was improvement in the ST segments and T waves somewhat earlier. In the four children who died, anterior force loss was obvious in three and suggestive in one initially. The delayed transitional zone persisted or extended in all four. In two, the pattern resembled that of an anterolateral infarct (Fig. 1). In the other two, the more impressive loss of force was inferoposterior. Both of these children developed a left axis deviation (−65° and −30°) during the follow-up period (Fig. 2). One of the two children with the anterolateral 'infarct' pattern showed massive fibrosis of the apex and lateral wall of the left ventricle at necropsy. Multiple areas of thrombus formation were present on the left ventricular endocardial surface, but no obvious coronary occlusion was found. Both children with the inferoposterior changes were examined at necropsy, and showed extensive thinning of most of the left ventricle, though the outflow and septal walls were less affected. All three infants showed the usual thickening of the endothelium, and all had involvement of the mitral valve structures.

Discussion

Although infarct patterns in infancy are rare, their appearance on the electrocardiogram is often of diagnostic value. They have been reported in children with myocarditis, cardiomyopathy, EFE, coronary calcinosis, and anomalous left coronary artery (Apley, 1961; Dominguez, Lendrum, and Pick, 1959; Noren *et al.*, 1964; Thomas *et al.*, 1956). The diagnosis of anomalous left coronary artery is usually the first to be entertained clinically when an infant under 1 year of age has evidence of significant myocardial damage on the electrocardiogram. Cardiac catheterization is usually done in infants presenting with heart failure, possibly caused by cardiomyopathy or myocarditis, specifically to rule out the possibility of an anomalous left coronary artery since this lesion is surgically correctable.

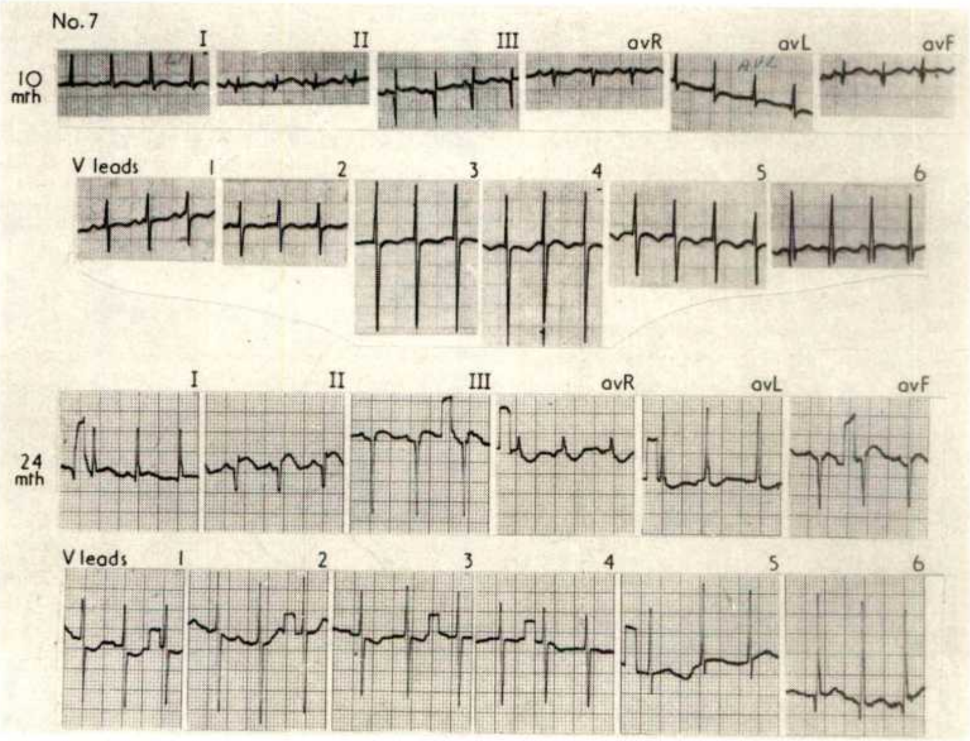

FIG. 2 *The admitting electrocardiogram at 10 months of age and an electrocardiogram at 24 months, just before phenolization, are shown for Case 7. Note the q waves in II, III, aVF, and V6 on the admitting electrocardiogram, with a delayed transition between V5-6. ST and T wave changes are not too striking. By 24 months of age, there are QS complexes in II, III, and aVF with a distinct left axis deviation. Transition occurs between V4-5 and ST changes are more pronounced.*

Although infarct patterns occur less often in EFE (Vlad, Rowe, and Keith, 1955), they have been reported in several cases. Of those reviewed, all but one of the children with myocardial damage on the electrocardiogram died (Hastreiter and Miller, 1964; Lintermans *et al.*, 1966; Ruttenberg *et al.*, 1964; Auld and Watson, 1957; Linde and Adams, 1963; Lambert and Vlad, 1958). In the one child who lived, the electrocardiogram was not reproduced in its entirety but showed ST elevation in the anterior praecordial leads with q waves in leads I and V6 (no q in aVL and no loss of anterior forces) (Linde and Adams, 1963). These cases plus the four children presented here suggest that the 'infarct' pattern when seen in children with EFE is a negative prognostic sign for survival. Some infants may die during the acute episode of failure without this finding on the electrocardiogram, but in those who survive the initial failure, there is a good correlation between the electrocardiogram and clinical course. At necropsy, there is often much fibrosis and thinning of the myocardium along with the typical endothelial thickening (Hastreiter and Miller, 1964; Letter, 1953; Thomas *et al.*, 1954; Marini and Pinca, 1962). With this type of damage, loss of electrical force may occur ('infarct patterns') and the conduction system may become secondarily involved (left anterior hemiblock, left posterior hemiblock, intraventricular conduction delays, etc.). If muscle is not destroyed completely or if damage is minor, then survival is likely and electrocardiographic abnormalities may be limited and reversible. Once the electrocardiogram shows a pattern of major loss, however, it is likely that the myocardial damage is severe and irreversible, and will result in death.

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Case reports

British Heart Journal, 1976, **38**, 523–525.

Origin of anterior descending branch of left coronary artery from pulmonary trunk

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Several cases of the left coronary artery originating anomalously from the pulmonary artery, such as the Bland-Garland-White syndrome (Bland, White, and Garland, 1933), or of the right coronary artery originating from the pulmonary artery (Tingelstad, Lower, and Eldredge, 1972; Wald *et al.*, 1971) have been reported. With the advent of coronary arteriography many other coronary anomalies (Ogden, 1970; Pachinger, Vanden Hoven, and Judkins, 1974) as well as fistulae between coronary arteries and heart chambers have been described (McNamara and Gross, 1969; Morgan *et al.*, 1972; Reddy, Gupta, and Hamby, 1974; De Nef, 1971).

We present here a rare anomaly which might be considered a variant of the Bland-Garland-White syndrome and which has not, to our knowledge, been reported previously.

Case report

A 35-year-old white woman was admitted to the cardiological clinic because of anginal symptoms for the past 17 years. On one occasion she had been told that she had a ventricular septal defect, because of a cardiac murmur. Several months before admission she had had atypical chest pain and dyspnoea on exertion. Interestingly, the chest discomfort occurred when entering a heated room from the cold open air.

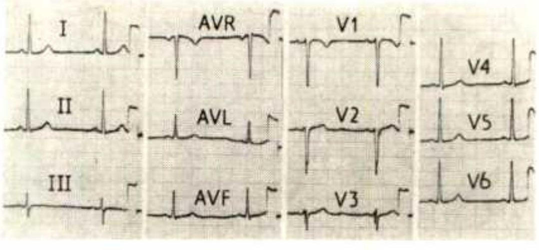

FIG. 1. *Electrocardiogram at rest.*

On examination the pulse rate was 90/min regular; blood pressure 110/80 mmHg (14·6/10·6 kPa); a systolic murmur could be heard over the base, without transmission, and a high frequency diastolic murmur over the apex. A third and fourth heart sound were present. Routine blood tests were within normal limits. The electrocardiogram (Fig. 1) showed no R wave progression from V1 to V3; chest x-ray examination was normal. The exercise tolerance on bicycle ergometry was reduced; the test was discontinued at 75 Watts because of dyspnoea, but no anginal symptoms were present at this level. Nevertheless, a significant ST segment depression suggestive of myocardial ischaemia was noted in leads I, II, and V3 to V6. Left and right heart catheterization showed a pulmonary artery pressure of

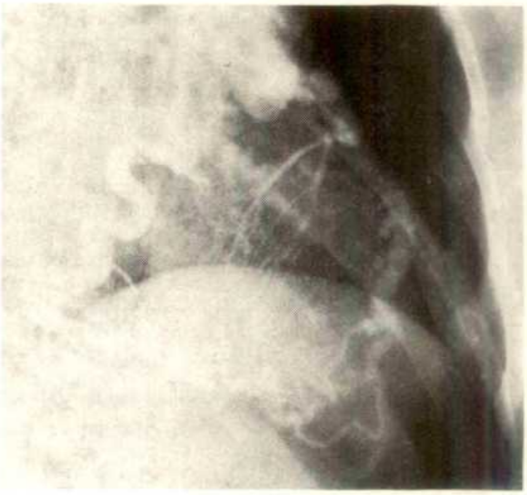

FIG. 2 *Selective angiogram of right coronary artery. The distal right coronary system provides good collateral circulation to anterior descending branch which empties into pulmonary artery.*

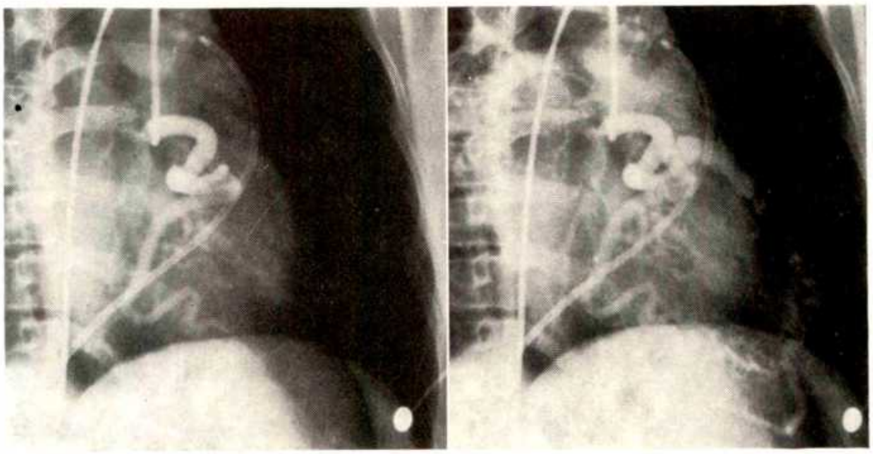
(a) (b)

FIG. 3 *(a) Selective catheterization of left coronary ostium shows large circumflex artery. (b) Circumflex artery provides rich collateral network to anomalous anterior descending branch.*

30/12/20 mmHg (4·0/1·6/2·7 kPa); the end-diastolic pressure in the left ventricle was 15 mmHg (2 kPa); dP/dt max 2040 mmHg/s (271 kPa), cardiac index 4·4 l/min per m^2 (AV difference 3·8 vol %). No oxygen saturation step-up in the pulmonary artery was found despite many measurements. Left ventriculography showed a normally contracting left ventricle; the ejection fraction was calculated at 70 per cent.

Coronary arteriography, performed by the Judkins technique, showed a right coronary artery arising from a normally situated ostium in the right sinus of Valsalva. The large and tortuous right coronary main stem followed the usual course in the atrioventricular groove and bifurcated at the crux into posterior descending and posterolateral systems. A large network of septal branches provided retrograde filling of the anterior descending coronary artery which terminated in the pulmonary artery (Fig. 2). Selective catheterization of the left coronary ostium showed the presence of a large circumflex artery (Fig. 3a) which also provided good collateral circulation to the left anterior descending branch via epicardial collateral vessels (Fig. 3b). It was impossible to visualize the anomalous left anterior descending artery with contrast medium injected into the main pulmonary trunk. However, injection of radioactive tracers confirmed the left-to-right shunt. Selective injection of ^{131}J-labelled microspheres into the right coronary artery resulted in activity not only of the inferior wall but also intense activity over both lungs. The injection of ^{99}Tc-labelled microspheres into the circumflex artery also revealed activity over both lungs.

Discussion

The coronary circulatory pattern in this case is a variant of the Bland-Garland-White syndrome. The anomalous origin of the left coronary artery from the pulmonary artery has been reviewed in a large series by Wesselhoeft (Wesselhoeft, Fawcett, and Johnson, 1968). The authors showed that in most cases the patient does not live more than 2 years. Therefore cases have been classified as infantile and post-infantile (Flamm *et al.,* 1968). The anomaly may be asymptomatic or anginal symptoms or signs of cardiac failure may develop. Mitral regurgitation is common and may be the main presenting sign (Burchell and Brown, 1962). The typical electrocardiographic features are left axis deviation, signs of left ventricular hypertrophy, evidence of myocardial infarction, or at least small q waves in leads I and aVL (Wesselhoeft *et al.,* 1968; Perry and Scott, 1970). None of these findings was present in our case. The only abnormality was the ST segment depression during bicycle ergometry.

The significant difference in coronary arterial anatomy between the classical Bland-Garland-White syndrome and the variation in our case is the presence of a dual coronary arterial supply (right coronary artery and circumflex artery) with two aortic sources. In cases of anomalous origin of the right coronary artery from the pulmonary artery (Tingelstad *et al.,* 1972; Cronk, Sinclair, and Rigdon, 1951; Wald *et al.,* 1971) the left ventricular myocardium is also supplied by two vessels (left anterior descending artery and circumflex coronary artery), but they have a single aortic source.

Possibly our patient did not develop severe symptoms because of the dual arterial supply and the sufficient collateral circulation. The lack of significant oxygen saturation step-up in the pulmonary artery is common with an anomalous left coronary artery (Wesselhoeft *et al.,* 1968; Perry and Scott, 1970). Perry reported a better prognosis in children who develop a significant left-to-right shunt, detectable by oxygen saturation within the pulmonary artery. In our patient the left-to-right shunt was demonstrated by radioactive tracers. Angiographic visualization of the anomalous left anterior descending branch by injecting contrast medium into the pulmonary artery could be obtained only rarely. Success seems to depend on an antegrade flow from the pulmonary artery to the aberrant vessel (Bookstein, 1964; Goldberger, 1960).

Surgical intervention has become feasible with the advent of bypass surgery and has been successful in patients with an anomalous origin of a left or right coronary artery from the pulmonary artery (Gasior *et al.*, 1971; Chaitman *et al.*, 1975; El-Said *et al.*, 1973; Tingelstad *et al.*, 1972; Barrand *et al.* 1975). The likelihood of sudden death has been the main indication for surgery in these patients (Wesselhoeft *et al.*, 1968; Wüthrich, 1951; Flamm *et al.*, 1968; Wright *et al.*, 1970). We did not consider surgery for our patient because of the absence of disabling angina pectoris and the presence of a dual coronary arterial supply providing excellent collateral circulation to the anomalous vessel.

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Cardiac abnormalities in chronic progressive external ophthalmoplegia

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This report describes heart disease in a 32-year-old man with the syndrome of chronic progressive external ophthalmoplegia (CPEO). The surface electrocardiogram showed first degree AV block and left bundle-branch block and there was HV prolongation on the His bundle electrogram. Endomyocardial biopsy showed the changes of hypertrophy on light microscopy, and on electron microscopy there were increased numbers of mitochondria which appeared structurally normal. A permanent demand pacemaker was inserted because these patients are prone to develop complete heart block.

Chronic progressive external ophthalmoplegia (CPEO) may be associated with pigmentary degeneration of the retina, ataxia, facial and limb weakness, and abnormalities of cardiac conduction which predispose to sudden premature death (Kearns, 1965; Drachman, 1968). Patients with complete heart block have been treated with permanent pacemakers (Ross *et al.*, 1969; Uppal, 1973). The most striking pathological findings in CPEO have been accumulation of abnormal mitochondria and considerable deposition of glycogen granules in skeletal and ocular muscle (Morgan-Hughes and Mair, 1973). In this case study we used His bundle recordings in assessing abnormal conduction in a patient with CPEO. The myocardial morphological changes were also studied by biopsy of endomyocardial tissue.

Case report

A 32-year-old man was referred because of his abnormal electrocardiogram. He had been known as 'Sleepy' from the age of 5 years because of bilateral ptosis. Impairment of voluntary eye movement began in adolescence, but this did not affect his physical activities. Throughout his adult life he had had recurrent corneal ulceration and had noticed some change in his facial appearance. There was no diplopia, loss of visual acuity, limb or girdle weakness, ataxia, or bulbar symptoms. Since July 1974 he had had six episodes of giddiness which were of sudden onset and from which he made a spontaneous recovery over one hour. There was no palpitation, chest pain, breathlessness, or loss of consciousness. When seen the heart rate was 80 per minute, regular, and the blood pressure was 130/80 mmHg (17·3/10·6 kPa). The second heart sound was widely split and varied normally with respiration, and he had a soft systolic murmur at the left sternal edge. General examination was otherwise normal. He was of normal intelligence. He had bilateral ptosis, a divergent squint, and there was a severe and slightly asymmetrical weakness of voluntary and reflex eye movements. The pupillary size and responses were normal. His visual fields and acuity were normal. There was a small right corneal ulcer. His fundi showed a peripheral pigmentary abnormality but the optic discs were normal. He had an asymmetrical facial weakness of lower motor neurone type but his jaw and lingual movements were normal. Palatal and pharyngeal sensation was normal but his pharyngeal reflexes were reduced. There was no muscle wasting or tenderness. He had weakness of neck movements and of all proximal shoulder girdle muscles with normal distal power in the limbs. There was no weakness of the pelvic girdle or lower limbs. The tone was normal and his tendon reflexes were reduced in the upper limbs with normal lower limb tendon reflexes and normal plantar responses. His left arm showed slight incoordination of rapidly alternating movements. His gait was normal. There were no sensory abnormalities.

Investigations

Creatine phosphokinase, aldolase, isocitrate dehydrogenase, gammaglutamyl transpeptidase, lactic dehydrogenase, aspartate transaminase, potassium, calcium creatine, urea, and electrolyte levels in the blood were normal. Haematological investigations included haemoglobin, white cell count, and ESR, all of which were normal. Serum thyroxine was normal. *X*-ray examinations of the skull, chest, and lumbosacral spine were normal.

Nerve conduction studies showed normal conduction in the left lateral popliteal nerve. Electromyography

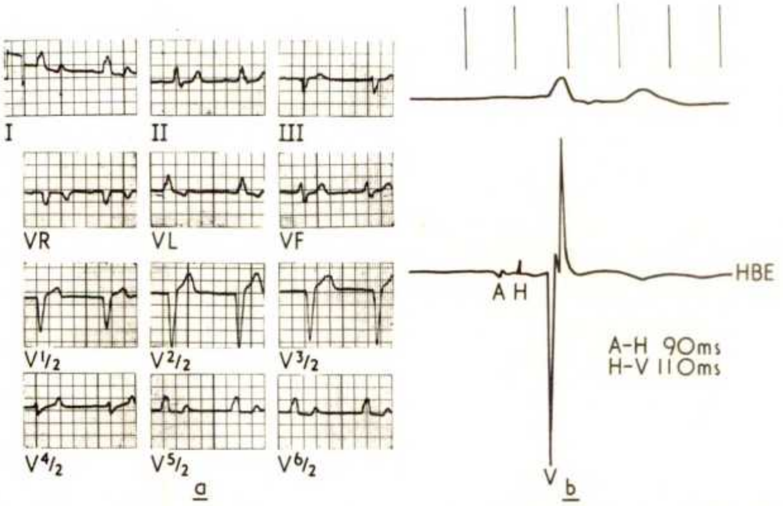

FIG. 1 *(a) Electrocardiogram showing first degree atrioventricular block and left bundle-branch block. (b) His bundle electrocardiogram showing prolonged HV interval. Time lines at* 200 *ms.*

showed a normal left tibialis anterior muscle, but there was an excessive number of small, short-duration polyphasic units in the left biceps muscle. Biopsy of tissue from the left triceps muscle showed some variation in fibre size and about 5 per cent of fibres showed mitochondrial accumulations. On electron microscopy the mitochondria were seen to contain paracrystalline inclusions and vacuoles and there was increased glycogen deposition around the mitochondria and between the myofibrils. The electroencephalogram was normal.

The electrocardiogram showed first degree atrioventricular block (PR interval 0·22 s) and left bundle-branch block (Fig. 1a). The echocardiogram was normal At cardiac catheterization all pressures were normal, including the left ventricular end-diastolic pressure, and there were no valvular abnormalities. The left ventriculogram was normal. His bundle recordings were obtained with a bipolar catheter positioned as previously described (Scherlag *et al.,* 1969). A simultaneous electrocardiogram and His bundle tracing are shown in Fig. 1b. During sinus rhythm the AH interval was 90 ms (normal range 80–190 ms) and the HV interval 110 ms (normal range 35–55 ms). Atrial pacing produced a sequential increase in the AH interval without altering the HV interval.

Right and left ventricular tissue for biopsy was obtained by the transfemoral percutaneous route. Light microscopy of the right ventricular specimen showed interstitial fibrosis with hypertrophy of the myocardial fibres and thickening of the endocardium to 40 μ (normal range up to 20 μ). Similar changes were seen in the left ventricular specimen with more distinct thickening of the endocardium. Electron microscopy showed regular arrangements of the myocardial fibrils with mitochondrial accumulation and increased glycogen deposition (Fig. 2). The mitochondria were structurally normal and the changes were indistinguishable from those of ordinary hypertrophy.

The patient gave his consent to the investigations, the nature of which was fully explained to him beforehand.

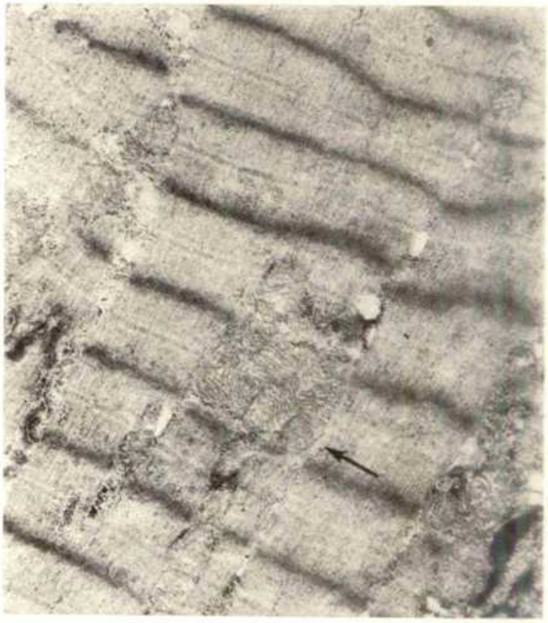

FIG. 2 *Right ventricular biopsy. Increased numbers of mitochondria which appear morphologically normal (arrowed).*

Management

A permanent demand pacemaker was inserted as a prophylactic measure.

Discussion

The variety of clinical associations of chronic progressive external ophthalmoplegia has led to uncertainty about the nature of the disease. The neurological component may be a primary myopathy (Kiloh and Nevin, 1951) or a denervation atrophy (Drachman *et al.*, 1969) or may represent the clinical manifestations of a single metabolic defect (Morgan-Hughes and Mair, 1973). No constant aetiological factor has been found. The nature of the involvement of the heart is equally uncertain. It has been called a cardiomyopathy (Uppal, 1973) but no histological changes have been described to support this contention. Postmortem studies have not been helpful (Jager *et al.*, 1960; Kearns, 1965).

The technique of percutaneous biopsy of the right and left ventricles of the heart is firmly established (Konno, Sekiguchi, and Sakakibara, 1971; Richardson, 1974). The endomyocardial biopsy in this patient showed changes not previously described in CPEO. The histological feature (regular arrangement of fibrils with mitochondrial accumulation and increased glycogen deposition) were of hypertrophy—an unexpected finding in this normotensive patient with no evidence of valvular heart disease. This finding may be significant in view of the changes found in ocular and skeletal muscle of this and other patients (Morgan-Hughes and Mair, 1973), which suggest that the mitochondria are intimately involved in the disease process. Cardiac involvement in other forms of muscular dystrophy includes abnormalities of the myocardium and conduction tissue. The myocardial involvement may lead to severe heart failure, as in the pseudohypertrophic type of muscular dystrophy and in Friedreich's ataxia (Taylor, 1974). The normal left ventricular pressures and ventriculogram and the abnormal intracardiac conduction in this patient emphasize that the cardiac involvement in CPEO is different as the conducting system bears the brunt of the disease process. Other manifestations of this cardiomyopathy may appear if prolonged survival occurs with pacing.

Patients with bifascicular block caused by chronic sclerodegenerative disease of the conducting tissue, such as right bundle-branch block and left anterior hemiblock, are known to develop complete heart block, the estimated risk being 6 per cent per year of follow-up (Kulbertus, 1973). In these patients this is not thought to be sufficient indication for the insertion of a prophylactic pacemaker. When such patients are further assessed by His bundle recordings a prolonged HV time, indicating delayed conduction in the His Purkinje system, may be found. To date, however, the value of such abnormal recordings in predicting the onset of complete heart block has not been established (De Pasquale and Bruno, 1974).

The conduction disturbance in CPEO seems to behave differently. These patients appear to progress from incomplete to complete heart block relatively often. Complete heart block has been preceded by right bundle-branch block and left anterior hemiblock in at least 5 cases and by isolated left bundle-branch block in one case (Drachman, 1968). In the only previously reported case of His bundle studies in CPEO (Morriss *et al.*, 1972) the patient had a prolonged HV time and developed second degree AV block (Mobitz type II) when given atropine. Subsequently, episodes of complete heart block occurred. In our patient the HV time was very prolonged and the surface electrocardiogram showed first degree atrioventricular block and left bundle-branch block (Fig. 1a). Though not an indication for pacing in sclerodegenerative disease of the conducting system (Scheinman, Weiss, and Kunkel, 1973), in the unusual group of patients with CPEO and conduction defects the prolonged HV time may be important in deciding to implant a permanent pacemaker even in the absence of symptoms.

We thank Professor C. D. Marsden for permission to study this patient, Dr. J. A. Morgan-Hughes for interpreting the skeletal muscle biopsy, and Dr. E. G. Olsen for interpreting the endomyocardial biopsy.

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Swedish Society of Cardiology and the British Cardiac Society

A Joint Meeting of the Swedish Society of Cardiology and the British Cardiac Society was held at the House of the Swedish Physicians in Stockholm from 31 August to 3 September 1975.

At the opening session a speech of welcome was made by the Chairman of the Swedish Society, H. Eliasch, to which the President of the British Cardiac Society, J. F. Goodwin, replied. An inaugural address on Carl Linnaeus was given by G. Strandell. The generous hospitality of the Swedish hosts included a dinner after the opening session, personal invitations to the homes of Swedish cardiologists, and dinner on the final evening. An official luncheon in Stockholm Town Hall on the closing day was preceded by visits to hospitals in the morning and followed by a boat trip in the Archipelago in the afternoon. A very enjoyable ladies' programme was organized by Mrs. Harald Eliasch. The excellent organization of the meeting was in the hands of the Secretary of the Swedish Society, L. Mogensen.

The scientific sessions included two symposia. The Moderator for 'The Prevention of Heart Disease' was G. Biörck and the speakers were June Lloyd, T. Lundman, M. Oliver, and L. Wilhelmsen. The Moderator for 'Physiological and Clinical Exercise Testing' was E. Sowton and the speakers were G. Blonquist, R. Edwards, B. Jonsson, and P. Sleight.

The following communications were given.

Abstracts

Pre-hospital coronary care provided by ambulancemen

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The experimental use in Brighton of coronary ambulances manned only by ambulance personnel has been continued and developed during 1974. The special equipment is portable and compact, and can be carried on any vehicle. The ambulancemen monitor the heart rhythm of patients carried in the ambulance, use a defibrillator if indicated, and also administer intravenous lignocaine or atropine in carefully defined circumstances. Electrocardiograms are also recorded on magnetic tape for subsequent analysis in the coronary care unit. Over 1000 patients were carried during the year, and approximately half were suffering from acute myocardial infarction or coronary insufficiency. More than 90 per cent of rhythm diagnoses were identified and interpreted correctly by the ambulancemen. Atropine was given 68 times and lignocaine 41 times; in all but one instance the indications were entirely as laid down. Fifteen patients were resuscitated successfully to be discharged from hospital alive. Fourteen of these had had ventricular fibrillation, and in six cases the cardiac arrest had occurred before the ambulance arrived.

Effects of cardioselective beta-blockers on chest pain, ECG, and heart function in acute myocardial infarction

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Catecholamines were found to increase the experimental infarction size in dog hearts *in situ* and aggravate the ischaemic damage of the isolated rat heart. During the first two days of acute myocardial infarction there might be an inappropriate sympathetic activity, as judged from shorter systolic time intervals (PEP and ICT) and higher systolic blood pressure and heart rate compared to normal controls. A reduction in sympathetic activity occurs during the first week of infarction. Beta-blockage therefore seems reasonable early in infarction to reduce myocardial ischaemia. Therefore, a single intravenous injection of practolol (ev. 18·2 mg) was given to 10 patients on the first day of AMI. This reduced systolic blood pressure and heart rate and prolonged the systolic time intervals to normal control values. No changes were seen in the left ventricular ejection time corrected for heart rates (LVETI) or in the raised a/H-ratio. All patients given practolol got an immediate relief of the chest pain. A double-blind study of 30 patients confirmed these effects of practolol in AMI. In two double-blind studies including 40 patients with acute myocardial infarction similar effects were obtained on heart work and chest pain by the cardioselective beta-adrenergic blockers H 87/07 (similar to practolol) and H 93/26 (cardioselective with no intrinsic activity). The beta-blockade also reduced ST segments in these patients with acute myocardial infarction.

The injection of cardioselective beta-adrenergic blockers was found to reduce heart work, ischaemic chest pain, and ST elevation in patients with AMI with no major side-effects. Prolonged beta-blockade during the first days of AMI might decrease the severity of myocardial ischaemia and limit the area of infarction as found in animal experiments.

Continuous recording of praecordial ST segment elevation during myocardial ischaemia

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Recent attempts to reduce the extent of necrosis after myocardial infarction have led to an interest in non-invasive methods of its assessment. The measurement of ST elevation from multiple praecordial sites has been used by many current methods of recording and analyses are cumbersome and not reproducible.

A system has been developed for the continuous recording on magnetic tape of the mean ST elevation from a maximum of 35 praecordial leads: on replay, a purpose-built computer provides further analysis and a running print-out of the sum of ST (ΣST). A simultaneous print-out of the heart rate has shown the relation between ΣST to rate change. This system has been compared to, and controlled by, a more orthodox measurement of a 35-lead ST praecordial map. The system has the advantage of preventing errors caused by repeated application of electrodes; of eliminating the subjective element in measurement; and providing relative convenience for the patients.

The natural history of ST segment variation has been studied over a 2-hour period in a group of patients admitted within 6 hours of symptoms of a heart attack. These results were described. In addition, the effect of antilipolytic treatment on the continuous recording of ΣST has been studied in patients within 6 hours of the onset of symptoms. The results from these studies indicate the value of this system in assessing any attempt to reduce the degree of acute myocardial ischaemia.

Prediction of mortality risk in acute myocardial infarction

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Serial serum estimations of total creatine kinase (CK) were obtained in 104 patients with acute myocardial infarction (AMI). Seventy of these had a history *without* a previous AMI. Relating the CK maximum to age, in this group, divided the patients into two subgroups, one with 49 per cent and the other with 3 per cent mortality during the hospital stay plus the next 90 days. This high or low mortality risk could be preducted in 68 of these 70 patients. Of 18 hospital and convalescence deaths, 17 could be correctly predicted, with an overprediction of 18 of the 50 survivors. This prediction could be done 3 to 8 hours after admission. The 34 patients *with* a previous AMI could also, relating CK maximum to age, be divided into two subgroups, one with 58 per cent and the other with 7 per cent mortality. These patients, however, were too few to permit prediction.

Myocardial scintigraphy with 99 mTc pyrophosphate and 201 tallium

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Sixty-five patients admitted to the coronary care unit with suspicion of acute myocardial infarction (AMI) received 10 mCi 99 mTc pyrophosphate and were examined in the left anterior oblique position with a mobile gamma camera (Portacamera, General Electrics), 12 to 120 hours after onset of symptoms. Two scintiscans were obtained initially at injection and then every 15 minutes during an hour, the scintigrams were evaluated with regard to uptake in the myocardial area. The localization was decided after contrast enhancement.

In 5 of 6 patients with angina pectoris, uptake was found. In 51 patients with a myocardial infarction uptake was found in 48. In 39 of these there was a good correlation between electrocardiographic and scintigraphic localization. Eight patients were discharged with other diagnoses and only one showed uptake.

In all patients with coronary heart disease a time course was observed with high initial uptake, which diminished on the 15- and 30-minute scintigrams, and another uptake starting to increase on the 45- and 60-minute scintigrams.

Five patients were also investigated with 201 Tl. A good correlation between the area of increased uptake with 99 mTc pyrophosphate and the region of decreased uptake with 201 Tl existed.

Formation of coronary arterial thrombi in relation to onset of necrosis in acute myocardial infarction in man: a clinical and autoradiographic study

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The presence of radioactivity in coronary arterial thrombi was studied at necropsy in 12 patients with acute myocardial infarction who had been given radio-labelled fibrinogen for the detection of deep venous thrombi. Seven patients received ^{125}I- and 5 patients ^{131}I-labelled fibrinogen. The radioactivity in the coronary thrombi was detected with autoradiography. With a short interval, below 10 hours, between onset of symptoms and injection of fibrinogen the entire thrombus was radioactive in 4 of 5 patients, whereas with longer time intervals only parts or none of the thrombus contained detectable radioactivity. The findings give further evidence that thrombus formation in acute myocardial infarction probably is a slow process and that the major part of the thrombus may form after the onset of necrosis.

Ventricular arrhythmias three weeks and one year after acute myocardial infarction (AMI)

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A hundred consecutive patients under 66 years treated for an AMI have been investigated for ventricular ectopic beats (VEBs) with electrocardiograms obtained by telemetry to an ink-jet writer. Registrations were performed before discharge three weeks after the AMI and one year later. Recordings consisted of three hours of daily activities and exercise and three hours at night. No routine antiarrhythmic therapy was given.

Three weeks after an AMI, VEBs were seen in 70 patients—34 of them had uniform only, 22 multiform only, a further 11 had paired VEBs, and another 2 showed the R/T phenomenon. One patient had ventricular tachycardia. VEBs were found in 59 per cent of night and 50 per cent of day recordings. The occurrence of VEBs was significantly associated with larger infarctions, reinfarction, ventricular tachycardia, or ventricular fibrillation during the acute phase.

To date 79 patients have been followed for one year. Ten have died, 4 instantaneously. Another patient had circulatory standstill but was resuscitated. A further 7 were not examined because of reinfarction. Sixty-one patients were reinvestigated for arrhythmia. The incidence of VEBs increased from 58 per cent to 77 per cent in patients who had a primary infarction whereas those with initial reinfarction had an incidence of 83 per cent on both occasions.

Procainamide and phenytoin: a comparison of two antiarrhythmic drugs

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In order further to evaluate procainamide and phenytoin, considering both efficacy and side-effects, some comparative studies on the two drugs have been performed. The antiarrhythmic effects were studied in 81 patients with suspected or proven myocardial infarction. Those patients who developed ventricular arrhythmia requiring treatment during the first 8 hours in hospital were randomly allocated to a procainamide or phenytoin group. Proposed therapeutic plasma levels were rapidly achieved by intravenous and oral loading doses. An electrocardiogram was continuously recorded during the 24-hour trial and analysed minute by minute. During the first 2 hours after initiation of therapy, a significantly higher frequency of therapeutic failure was found in the phenytoin group (23 of 35 patients) compared with the procainamide group (13 of 39 patients). Also side-effects were more frequent in the phenytoin group. The haemodynamic effects of the two drugs, given intravenously during conventional cardiac catheterization on 19 patients with congenital heart defects, have also been studied. With equipotent plasma concentrations of the drugs phenytoin had the most pronounced negative inotrophic effect.

Thus, the results of these investigations show the overall advantage of procainamide over phenytoin during short-term therapy after acute myocardial infarction.

Analysis of preoperative and operative factors influencing outcome of aortocoronary bypass surgery in 146 patients

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Thirty-five (24%) of 146 consecutive patients followed for at least 6 months (mean 13·4 months) had recurrent angina after coronary artery bypass. They were compared with the asymptomatic group to determine which pre- and intra-operative factors are important in the recurrence of angina. There was no difference in the preoperative age, sex, duration or grade of angina, mean serum cholesterol, incidence of myocardial infarction, or graft flow. The maximum level in the preoperative exercise and the maximum pacing rate were higher in the asymptomatic group ($P < 0{\cdot}01$ and $P < 0{\cdot}05$, respectively). Left ventricular end-diastolic pressure, left ventricular angiographic, and total coronary scores were similar in the two groups, but there were fewer coronary scores of 10 and 11 (of 12) in the angina group ($P < 0{\cdot}025$).

The angina-free group had more grafts ($P < 0{\cdot}025$), and more left ventricles were judged normal at operation ($P < 0{\cdot}01$). Scoring grafted vessels as zero, they had a lower coronary score after operation ($P < 0{\cdot}01$), and more had zero scores ($P < 0{\cdot}01$). All postoperative myocardial infarcts occurred in the patients with angina.

We conclude that the degree of revascularization is the most important factor in determining the outcome. Patients with demonstrably good stress tolerance are more likely to be relieved of angina. The occurrence of clinical postoperative myocardial infarction has an adverse effect.

Evaluation of early and long-term function of aortocoronary saphenous vein grafts

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During the past 3 years, 180 patients (with 310 grafts) underwent repeat angiography after aortocoronary saphenous vein bypass graft operations. This constitutes 40 per cent of the total number of patients undergoing this operation at Harefield Hospital and included routine restudies as well as patients with residual or recurrent symptoms.

The overall graft patency rate was 91 per cent while 96 per cent of the patients had 1 or more patent grafts. The patency rate in patients studied during the first 3 months after operation was 96 per cent while in those studied 4 months to 4½ years the patency rate was 82 per cent. There was no difference in the patency rate of grafts to different coronary vessels. Additional gas endarterectomy (performed in 25% of the cases), diabetes, hypertension, previous infarcts, or venosclerosis affecting the saphenous vein did not seem to affect the patency rate. There was no evidence of progressive dilatation or narrowing of the grafts. Left ventricular function, assessed by ventriculography did not change in the majority of patients, though in some cases there was improvement in ejection fraction and pattern of left ventricular contraction. There was no evidence of significant accelerated progress in the native vessel disease.

It is concluded that aortocoronary saphenous vein grafts continue to function satisfactorily for periods of up to 4½ years.

Haemodynamic long-term follow-up of patients with aortic valvular disease

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In an attempt to find measurements of prognostic significance 128 patients with aortic valvular disease were studied by repeated graded exercise tests including determinations of cardiac output. The patients were forced to the limit of tolerance with exhaustion, excessive dyspnoea, or intense angina pectoris as restricting factors. More than 400 exercise tests of this kind have been performed without serious complications. Normal physical working capacity (PWC) was defined as 600/900 kpm/min (women and men, respectively) during at least 4·5 minutes.

The courses were poorly correlated to aortic valvular area, degree of regurgitation, left intraventricular pressures, heart enlargement, and electrocardiographic abnormalities. Patients with a normal PWC attaining effective stroke volume index (SVI) above 50 ml/m^2 and cardiac index (CI) more than 7 l/min per m^2 on maximal load, had an unchanged course during 3 to 5 years, while those with SVI and CI below these limits deteriorated clinically and haemodynamically during the subsequent 1 to 3 years. Patients with subnormal PWC and effective SVI around or below 40 ml/m^2 on maximal load had a bad prognosis with further deterioration and even sudden death (11 cases) within less than one year. Some younger patients with SVI exceeding 40 ml/m^2 were improved, while others presented an unchanged course or deteriorated in parallel to a reduction of SVI below 40 ml/m^2 on maximal load.

Influence of preoperative left ventricular function on results of homograft replacement of aortic valve for aortic stenosis

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The effect of preoperative left ventricular function on early and late prognosis was assessed in 50 consecutive patients with aortic stenosis, who underwent left ventricular angiography before homograft replacement of the aortic valve. Patients were divided into 2 groups, those with a left ventricular ejection fraction of 0·46 or more (group A), and those with an ejection fraction of 0·45 or less (group B). Other indices of poor left ventricular function in group B included a low cardiac index with raised left ventricular end-diastolic pressure. Group A consisted of 29 patients, with a mean age of 52 years, and group B of 21 patients, with a mean age of 55 years.

There were no operative deaths in either group and no late deaths in group A. One patient in group B (4%) died late. The length of follow-up varied from 3 months to 5½ years. Symptomatic improvement was observed in all patients in both groups. Ninety per cent of patients in group A moved to Class I of New York Heart Association Classification compared with 70 per cent of group B. Regression of electrocardiographic and radiological signs of left ventricular hypertrophy were more consistent in group A. Repeat angiography in 10 patients of group B showed improvement of ejection fraction in 7.

It is concluded that poor left ventricular function in patients with aortic stenosis does not increase the risk of homograft valve replacement. Though many patients with poor left ventricular function derive considerable benefit from the operation, the overall improvement and probably the long-term survival is less than in patients with good left ventricular function.

Aortic valvular surgery using hypothermia without coronary perfusion

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At the University Hospital of Lund aortic valvular surgery has been performed since 1970 using Björck-Shiley disc prosthesis inserted under local hypothermia with the aid of 'Bretschneider's solution', making coronary perfusion unnecessary. This paper deals with the first 50 patients operated in this way. The preoperative mortality was 8 per cent (4 patients). A further 8 patients died from a variety of causes during the next 6 months.

The paper comprises: (1) a brief description of the method used, and (2) a comparison between preoperative findings and results obtained one year postoperatively in 38 patients, including physical working capacity (PWC), haemodynamics during maximal work load (cardiac index, CI; stroke volume index, SVI; and intra-arterial blood pressures), electrocardiographic abnormalities, and radiological heart size.

In summary there was a significant increase of PWC, a striking improvement of CI and SVI on maximal work load, a significant regression of electrocardiographic signs of left ventricular hypertrophy and strain, and a reduction of heart size in most patients. Angina pectoris which was a common symptom preoperatively was seen in only 3 patients one year after operation.

Pulmonary autograft for aortic valve disease: 3 to 8 years later

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Between 1967 and 1971, 100 patients, aged 12 to 54 years, whose diseased aortic valve was replaced by their own pulmonary valve (autograft) and a cadaveric aortic homograft placed in the right outflow, have been followed for 3 to 8 years with haemodynamic studies. Of these, 65 had operation for lone or dominant aortic regurgitation and 35 had severe stenosis. After operation important aortic regurgitation occurred in 16, dating from early postoperative weeks in the majority and in patients operated on for serious aortic regurgitation. Re-operation (6%) constantly confirmed malpositioning of autograft. Acute valve failure occurred in one patient—the only patient in whom a frame-mount was used. Late mortality was low (5) and so was the incidence of bacterial endocarditis (3). There was no haemolysis or gradients above 10 mmHg (1·3 kPa) across the autograft; neither was there progressive obstruction on either side of the heart nor need for anticoagulants. There was a slight increase in aortic regurgitation in those in whom it was present after operation after 5 years. Trivial diastolic murmurs occurred in 56 patients without evidence of important or increased pulmonary or aortic regurgitation. Histology in the few autografts examined suggests the presence of living cells in the valve up to five years after operation. In spite of the higher early mortality in comparison with other forms of aortic valve replacement and the added morbidity from the right-sided homograft, the low incidence of late complications suggests this may be the best aortic valve replacement, particularly in the young patient.

Plasma aldosterone levels in patients with severe, treated heart failure

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The availability of patent aldosterone antagonists has raised the question of the incidence and importance of hyperaldosteronism in congestive heart failure. The development of a sensitive method for aldosterone, based on radio-immunoassay, has allowed us to study the plasma levels of this hormone in patients with severe treated heart failure. The findings have been correlated with plasma levels and total exchangeable sodium and potassium by radioisotope dilution methods: in some patients extracellular fluid volume was also measured as the sulphate space.

Twenty-five patients were studied in a stable state on unmodified optimal treatment, mostly while awaiting valve replacement.

The plasma aldosterone was ten times the normal level in some patients. The changes were related to the severity of the heart failure, as judged by the right atrial pressure at cardiac catheterization ($r=0{\cdot}63$), the fall in total exchangeable potassium ($r=0{\cdot}60$), and the intensity of diuretic treatment measured as a daily dose of frusemide ($r=0{\cdot}77$). There was little relation to the plasma electrolyte changes.

Although aldosterone antagonists are useful to maintain plasma potassium levels during intensive diuretic therapy, the effect on tissue electrolytes is complex, and may not be entirely beneficial.

Prolonged hyperaldosteronism may be a factor in the production of cardiac cachexia and the loss of cellular potassium cannot necessarily be replaced by supplements in this situation.

Consideration should be given to possible surgical treatment before heart failure reaches this degree of severity.

Echocardiographic diagnosis of primitive ventricle

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Recent morphological studies in our institute have shown that the pathognomonic feature of 'primitive ventricle' (considered by us to be a better term than any of the synonyms 'single', 'common', or 'double inlet left' ventricle) is absence of the posterior segment of the interventricular septum. The anterior part of the septum may or may not be present. When present, it, together with a bulboventricular ridge, forms an anterior or bulboventricular septum. This feature enables the condition to be classified into primitive ventricle with or without an outlet chamber. While presence of this outlet chamber is of significance, and can be established angiographically, knowledge of the presence or absence of a posterior septum separating the atrioventricular orifices is of paramount importance to subsequent surgical management. In our experience this diagnostic feature cannot be unequivocally proven using angiographic techniques. However, use of strip chart, single beam M mode echocardiography enables presence or absence of this part of the septum to be elucidated. When the posterior septum is absent, the septal cusps of the atrioventricular valves approximate each other during diastole. In contrast, when the septum is present the typical bilaminar septal echoes are seen separating the echoes from the valve septal cusps.

We have found this technique of considerable value in distinguishing between the diagnoses of transposition with ventricular septal defect and primitive ventricle or double outlet right ventricle and primitive ventricle. In addition, the technique has enabled deformities of one or other atrioventricular valve to be identified in primitive ventricle, again a matter of considerable importance in determining future surgical management of the anomaly.

Value of echocardiography in diagnosis of congenital mitral stenosis

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Ten patients with congenital mitral stenosis have been studied by conventional single element echocardiography. The diagnosis was verified at operation or necropsy in 9 patients. One of the patients had an isolated congenital mitral stenosis. In the other patients this lesion was combined with different congenital heart malformations (coarctation of the aorta 6 patients, ventricular septal defect, and/or persistent ductus arteriosus 3 patients). Three patients were operated upon with a mitral valvotomy together with a correction of the associated heart malformation.

The first echocardiographic examination was in 5 patients performed during the first year of life. The deviations from normal in the echocardiogram consisted of a reduced closing velocity of the anterior mitral leaflet during the rapid filling period in diastole and a more or less reduced amplitude of opening movement of the anterior mitral leaflet in the beginning of diastole.

In all patients it was possible to diagnose the mitral stenosis by echocardiography and to separate those with a severe degree of stenosis from those where the degree of stenosis was slight. A clearly reduced amplitude of movement seems to indicate that it is not possible to perform only a mitral valvotomy.

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Repair of mitral regurgitation in paediatric age-group

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Between May 1971 and December 1974, 25 infants and children aged between 7 months and 14 years (8 were below the age of 4 years) presented with severe mitral regurgitation. A reconstructive valve-conserving operation was performed in all patients except 1, who was treated by homograft valve replacement. The aetiology of the valve disease was congenital in 13 and rheumatic in 5 patients. Associated lesions included atrioventricular defects in 5, 1 or whom had a complete atrioventricular canal, Marfan's syndrome in 1, ventricular septal defect in 2, and corrected transposition with Ebstein's anomaly in 1 patient. Severe pulmonary hypertension was present in 10 patients.

Surface-induced profound hypothermia was used in 5 patients. There were no operative or late deaths. One child had residual cerebral damage.

Clinical evaluation with a follow-up period of 3 months to 4 years (mean 23 months) showed evidence of good correction of the lesion in all but 1 patient who has the signs of residual moderate mitral regurgitation.

It is concluded that conservation of the valve is possible in the majority of infants and children with severe mitral regurgitation. The early and late results of this procedure have been encouraging.

Repair of ventricular septal defects in infancy

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Between May 1971 and March 1975, 31 infants under 1 year of age underwent closure of a ventricular septal defect at the Hospital for Sick Children, Great Ormond Street, London. Their weight ranged from 2·5 kg to 6·5 kg (mean of 4·6 kg). The indication for surgery was intractable heart failure in spite of maximal medical support. An inadequate banding of the pulmonary artery had been done in 7 of the infants before closure of the ventricular septal defect. All the patients had a left-to-right shunt greater than 2:1, pulmonary hypertension (Pp/Ps greater than 0·6), and normal pulmonary vascular resistance. There were associated cardiac anomalies in 12 cases. Both the techniques of circulatory arrest, with deep hypothermia and conventional cardiopulmonary bypass were used. The defects were closed through a right atriotomy or a right ventriculotomy. There were no operative deaths and one late death which was not related to the cardiac disease. The ventricular septal defect reopened in 2 cases, one of which was reoperated successfully.

Our current policy is to close the ventricular septal defects with large left-to-right shunts rather than to band the pulmonary artery when the infants fail to improve with medical treatment.

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Congenitally corrected transposition of the great arteries: a clinical study of 101 cases

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The anatomy, natural history, clinical features, and symptomatology of 101 cases of congenitally corrected transposition of the great arteries (C-TGA) diagnosed over a 20-year period at The Hospital for Sick Children, Toronto, Ontario, is reported. Only 1 patient had no associated lesion and only 14 an intact ventricular septum. Pulmonary stenosis was present in a little less than half of the patients. Left AV valve involvement existed in 21 patients.

In spite of the high incidence of associated lesions the prognosis was better than expected. Seventy-six patients were alive at the end of the study, no one being critically ill. No death occurred among the patients with intact ventricular septum. Patients with pulmonary stenosis as a group developed symptoms later, were less handicapped, and had a better prognosis than those without a pulmonary stenosis. One-third of the patients had dysrhythmias. Eight patients had a 3rd degree AV block.

Auscultatory findings were not very helpful when diagnosing C-TGA. Forty-seven patients had a single second sound; of these, 37 had pulmonary stenosis. In 60 per cent of the patients, where information was available, the second sound was reported to be of normal intensity.

Our surgical experience is documented and discussed. Palliative procedures were done with successful results and low mortality. Totally corrective procedures were performed in 9 patients with 4 deaths.

Association of secundum atrial septal defect with abnormalities of atrioventricular conduction or left axis deviation: a new syndrome

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A genetic analysis was made of 10 families in which the propositi had a secundum atrial septal defect associated with abnormal atrioventricular conduction (first, second, or third degree heart block) or unexplained left axis deviation, or a combination of these conduction disturbances. Diagnostic information was available on 51 (81%) of the 63 first degree relatives.

Three of the families appeared to be examples of a new syndrome which, with variable expression, was inherited as a non sex-linked autosomal dominant. The main features were a secundum atrial septal defect, disease of the conducting tissue, which in some cases was progressive, unexplained left axis deviation, and unexpected death. These families did not appear to be examples of the Holt Oram syndrome for the upper limbs were clinically and radiologically normal in the 19 members examined.

The importance of recognizing this syndrome is the occurrence of progressive disease of the conducting tissue and the risk of sudden death.

In the remaining 7 families there was only one affected first degree relative out of 39 examined. He was the son of one of the propositi and had paroxysmal coronary sinus rhythm with an intact atrial septum.

Effect of therapeutic doses of lignocaine hydrochloride on effective refractory period of right ventricle in humans

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The effect of lignocaine on the effective refractory period of the right ventricle (EVRP) was measured in 10 patients using the extra-stimulus technique of progressive introduction of premature stimuli until a response could not be elicited. In 4 patients lignocaine produced a significant decrease in the EVRP, in a further 4 patients there was no change in EVRP, and in the remaining 2 patients lignocaine produced a significant increase in the EVRP. The effect of the drug on the EVRP could not be correlated with the serum potassium levels.

The reasons for the variable effect of lignocaine are attributed to the different action of lignocaine on different components of conduction within the ventricle.

Electrophysiological properties of right atrium in relation to physical training and heart rate

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The monophasic action potential (MAP) and the effective refractory period (ERP) of the right atrium were determined in eight healthy volunteers before and after hard physical training. The duration and amplitude of the MAP increased in seven individuals after training. ERP showed no consistent changes. One possible explanation for the findings is an accumulation of intracellular potassium. The duration of the MAP was well correlated to maximal heart rate.

Management of paroxysmal supraventricular tachycardia using a scanning pacing system

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Programmed stimulation of the heart has shown that a re-entry process is commonly the mechanism of supraventricular tachycardias. Under these circumstances it is usually possible to terminate the tachycardia by suitably timed premature beats. However, it has been found in any one patient that the point at which premature beats can terminate a tachycardia varies over 20 to 30 ms. This means that premature beats with preset coupling times cannot be relied on consistently to terminate an attack. A pacing system has, therefore, been developed which is automatically activated when tachycardia occurs and induces single or double atrial or ventricular premature stimuli with a preset coupling time. The first stimulus occurs within the refractory period of the stimulated chamber, then one second later a second stimulus is induced but is delayed by 5 ms. Five millisecond increments in delay occur every second until 100 ms has been scanned. When the tachycardia is terminated stimulation ceases. This scan can occur using either single or double stimuli. Two patients with intractable supraventricular tachycardia have been fitted with a Devices 4273 miniscan. In one patient the cardiac cycle is scanned with single ventricular premature beats and in the other double ventricular premature beats In both patients their tachycardias are now consistently terminated within 5 to 20 seconds of the spontaneous onset of the tachycardia.

Ultrastructural investigation of cardiac biopsies

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and Malmö allmänna sjukhus, Malmo

Twenty-five patients who underwent complete cardiac investigation including endomyocardial biopsy from the right ventricle are presented. The clinical and haemodynamic findings are presented together with comments on the biopsy method used. Special attention is given to the ultrastructural changes, with particular reference to the occurrence of artefacts. Different fixation methods have been used in order to obtain an optimal result from a technical point of view. Careful and uniform handling of the tissue samples seems to increase the theoretical as well as the practical usefulness of cardiac biopsy. On the basis of our experience in more than 150 cases the method used is considered simple, reliable, and safe.

Adaptation of left ventricle to sudden changes in heart rate in patients with artificial pacemakers

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In five patients treated with external pacemaker for complete heart block, the adaptation of left ventricular volume to sudden changes in ventricular rate has been analysed on a beat-to-beat basis, by one-plane cineangiocardiography and simultaneous aortic pressure recordings. The results are unambiguous and show: (1) When heart rate is changed above a certain lower limit left ventricular stroke volume varies inversely with heart rate. (2) The changes in stroke volume are brought about by changes in left ventricular end-diastolic volume proportionate to the duration of mechanical diastole and filling energy. The end-diastolic volume is unchanged. (3) Left ventricular end-diastolic volume and stroke volume adapt, on a beat-to-beat basis, to changes in heart rate. (4) There is a lower border frequency at which the ventricular end-diastolic volume is maximal. Below this frequency, a further increase in length of diastole does not increase the stroke volume.

Functional defect in amyloid heart disease 'the stiff heart syndrome'

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Royal Postgraduate Medical School, London W12 0HS

Left ventricular performance was studied in three patients with heart failure as a result of amyloid. The diagnosis was proven by cardiac biopsy in 2 patients and by rectal biopsy in the third.

The left ventricular diastolic pressure was high throughout diastole and exceeded the pressure in the right ventricle by at least 10 mmHg (1·3 kPa) in each case. Pressures were recorded through a catheter tip manometer during injection of contrast medium into the left ventricle allowing simultaneous volume measurement. The left ventricular volumes were not increased at end-diastole (62–118/m^2) despite very low ejection fractions (between 40 and 43%). The left ventricle was shown to be stiff since for each diastolic volume the pressure was higher than normal and for each volume change (ΔP) was greater than normal.

The unyielding poorly contracting and slowly filling left ventricle explains the low stroke output and hypotension. The left ventricular angiogram showed normal contours but coarsened trabeculation and prominent papillary muscles.

Both the functional defect and the angiographic appearance are unique to amyloid and differ from the dysfunction caused by other known disorders of the myocardium, the generalized systolic impairment of dilated cardiomyopathy, the focal faults caused by coronary artery disease and the diastolic abnormalities of hypertrophic cardiomyopathy, restrictive cardiomyopathy, and constrictive pericarditis.

Left ventricular pressure-volume relations in hypertrophic cardiomyopathy, with effect of beta blockade

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Left ventricular diastolic compliance was studied in 8 patients with hypertrophic cardiomyopathy (HOCM) of the left ventricle, before and after the intravenous administration of 0·3 mg practolol per kg body weight. Simultaneous measurements of left ventricular pressure and volume were made throughout ventricular diastole. The pressures were recorded as contrast medium was injected into the left ventricle through a catheter sheath surrounding a catheter-tip manometer. Left ventricular volumes, calculated by planimetry from the right anterior oblique cineangiogram were directly related to the simultaneously recorded pressures by a linking system. Peak positive and peak negative dP/dt were also determined.

Analysis of the pressure volume data showed that the relation in this condition could be expressed as a straight line ($P = aV + b$) with a high degree of accuracy both in the control state and after practolol administration (mean R value 0·95). Practolol produced no consistent alteration in the slope (a), but uniformly depressed the pressure intercept (b) mean change 6·7 mmHg (0·9 kPa). Peak negative dP/dt increased (mean 274) after practolol. Peak positive dP/dt did not alter.

It is concluded that the diastolic pressure volume relation in HOCM is linear within the limits of pressure and volume encountered and that it is unnecessary to use an exponential or other complex function to describe it, as well as being theoretically unsound.

We have shown that practolol accelerates relaxation of the series elastic element of the myocardial muscle fibre but that it does not alter compliance $\left(\frac{\Delta P}{\Delta V}\right)$. Contractile function as indicated by dP/dt and ejection fraction appears to be unaffected by practolol.

Chronic beta-adrenergic receptor blockade in congestive cardiomyopathy

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Conventional therapy in congestive cardiomyopathy has failed to change the final outcome of the disease. The treatment has been so unsatisfactory that cardiac transplantation might be considered in desperate cases. In a recent study immediate relief of ischaemic chest pain was reported when beta-blocking agents were given to patients with acute myocardial infarction. In some patients with high heart rate the injection of beta-blockade was followed by disappearance of the signs of left-sided backward heart failure.

In the present study adrenergic beta-blocking agents were, therefore, given to seven patients with advanced congestive cardiomyopathy who had tachycardia at rest (98±13 beats/min). The patients were on beta-adrenergic receptor blockade for 2 to 12 months (av. 5·4 months). One patient was given alprenolol, 50 mg twice daily, and the other patients were given practolol, 50–400 mg twice daily. Virus infection was seen in six of the patients before the onset of symptoms of cardiac disease. All patients were in steady state or were progressively deteriorating at the start of beta-adrenergic receptor blockade. Conventional treatment with digitalis and diuretics was unaltered or reduced during treatment with beta-blocking agents. A striking improvement was seen in their clinical condition shortly after administration of the drugs. Chronic treatment resulted in an increase in physical working capacity and a reduction of heart size.

Noninvasive investigations including phonocardiogram, cartoid pulse curve, apex cardiogram, and echocardiogram showed improved ventricular function in all cases. The present study indicates that adrenergic beta-blocking agents can improve heart function in at least some patients with congestive cardiomyopathy. Furthermore, it is suggested that the presence of catecholamines may be an important factor for the development of this disease, as has been shown in animal experiments.

Viscous properties of cat myocardium

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The measurement of ventricular diastolic compliance is complicated by the presence of viscous properties. However, quantitative assessment of these properties has not been made. In order to approach this problem, cat papillary muscles contracting isometrically at 15/min at 26°C were stretched at different velocities during diastole. At a given length there was no excess of force above that defined by the static force-length curve until velocity of stretch exceeded one muscle length/second. At greater velocities of stretch there was an increase of force with increasing velocity of stretch denoting viscous resistance to stretch. This viscous resistance to stretch increased with muscle length. At a given muscle length potentiation of contractile state by paired pulse stimulation caused a change in the diastolic force length curve but no apparent change in viscous resistance to stretch, ie there was no apparent relation between viscous resistance to stretch and contractile state or the length of the 'series viscous element'. These results would lead one to expect viscous resistance to stretch during rapid filling of the intact left ventricle.

Correspondence

British Heart Journal, 1976, 38, 539.

A policy for hypertension

Sir:

In a leading article (*British Heart Journal*, 1975, 27, 893) you say disapprovingly that it has been widely inferred that 'substantial reductions in mortality and morbidity can be expected from effective treatment of mildly raised blood-pressure (diastolic 95–110 mmHg)' and you cite a *Lancet* leader as source of this quoted passage. In the original the passage was prefaced by a ponderous but unmistakable qualification: 'Although the case is far from proven, the indications are that . . .'. Unhappily this qualification does not appear, even with leavening, in your own article. Elsewhere you cite our leader as suggesting that 'all those with a diastolic pressure of 95 mmHg or over should be on hypertensive therapy . . .'. We made no such suggestion. In our editorial (entitled Home Blood-pressure Recording) we said that this group may comprise 15 to 20 per cent of the adult population, 'and if it is true that all these patients are at increased risk and would benefit from therapy then an enormous work-load will be generated.' This is a far cry from a general summons to the dispensary. As we said on 11 October (Shall I Treat Mild Hypertension?), 'to embark on widespread treatment, without solid evidence of efficacy, might be costly folly'.

Ian Douglas-Wilson,
Editor,
The Lancet,
7 Adam Street,
London WC2N 6AD.

This letter was shown to Dr. Short who replies as follows:

Sir:

I am grateful to the Editor of the *Lancet* for clarifying his attitude to the treatment of mildly raised blood pressure. When I first read the Leading Article in the *Lancet* (1975, **1**, 259) it seemed that it would be widely interpreted as encouraging the treatment of mild hypertension—a course of action which in my view is entirely unjustified. Moreover, I consider that it was misleading to cite the Framingham study in support of this attitude, since the Framingham study dealt with the risks of hypertension and not with the benefits of treatment. I criticized the Leading Article at the time it appeared (*Lancet*, 1975, **1**, 531) and this criticism has, to my knowledge, never been answered in that periodical.

On rereading the Leading Article with the Editor's observations in mind, I still feel it gives the impression that antihypertensive treatment should be seriously considered in anyone with a diastolic blood pressure of 95 mmHg (12·6 kPa) or more. I am glad to be assured that this is not the view of the Editor.

David Short,
Cardiac Department,
Aberdeen Royal Infirmary,
Foresterhill,
Aberdeen.

British Heart Journal, 1976, **38**, 540.

Myocardial infarction in young men
Study of risk factors in nine countries

Sir:

We read with interest the prospective multicentre study of risk factors in coronary artery disease from 9 countries (Dolder and Oliver, 1975, *British Heart Journal*, **37**, 493). In Poona (India), which is only 100 miles from Bombay, we carried out a similar prospective study of the risk factors in precocious coronary artery disease (Wadia *et al.*, 1973). We had 90 patients with coronary heart disease below 40 years of age, comprising 40 with infarction and 50 without infarction. The risk factors were similar in the 2 groups and so we analysed the 90 patients together.

The commonest factor was smoking. Of the 76 per cent who were smokers 65 per cent had smoked more than 10 cigarettes a day for 15 years or more; 5 per cent chewed tobacco excessively without any smoking. A serum cholesterol value above 7·12 mmol/l (275 mg/100 ml) was found in 27 per cent of the group. The difference may be partially explained by the fact that we took our samples between 1 and 3 weeks after admission to hospital. But it may also be because our cases were from a private paying clinic and, therefore, represented a higher socioeconomic group than those from the municipal free hospital in Bombay, from where the other series was presumably drawn.

The glucose tolerance test in the third week was abnormal in 15 cases: 1 h>6·7 mmol/l; 2h>8·9 mmol/l (1 h>120 mg/100 ml: 2 h>160 mg/100 ml). Hypertension (diastolic over 95 mmHg (12·6 kPa) was noted in 23 per cent and a family history of coronary artery disease was found in 26 per cent of our cases. We found none of the following 6 risk factors in 17 of our 90 patients: smoking, hypercholesterolaemia, a diabetic glucose tolerance test, hypertension, family history, or high uric acid. Only 1 risk factor was present in 30 (in 20 smoking was the only risk factor), 2 risk factors were present in 17, 3 risk factors in 10, and more than 3 risk factors in 16 cases. None of our patients had a blood uric acid level above 0·5 mmol/l (8·5 mg/100 ml).

R. S. Wadia, R. B. Gulati, P. M. Soares, and K. B. Grant,

Ruby Hall Clinic,
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Poona, India.

Reference

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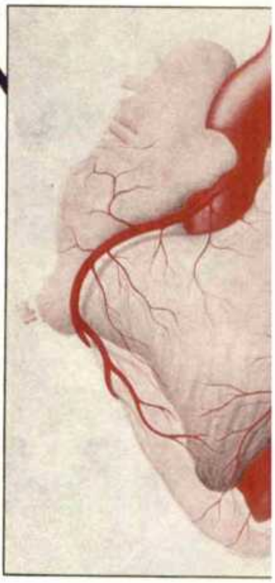

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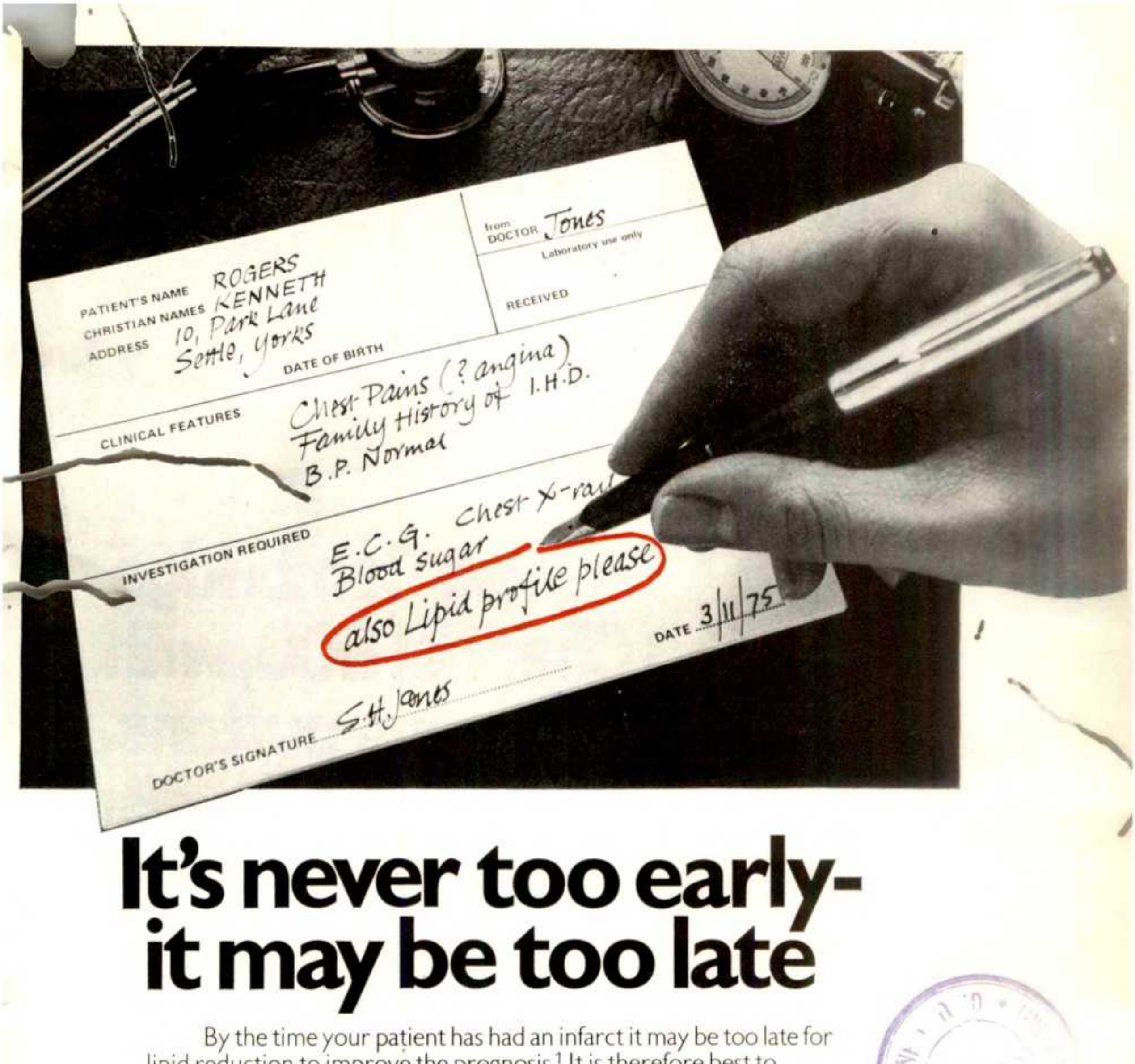

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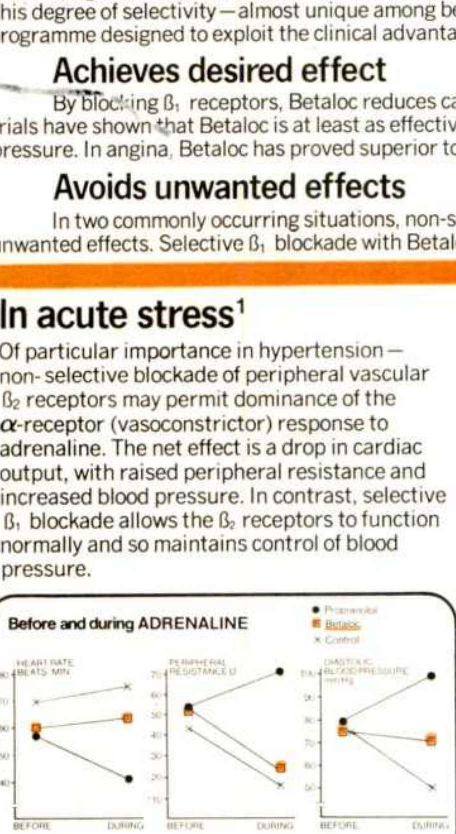

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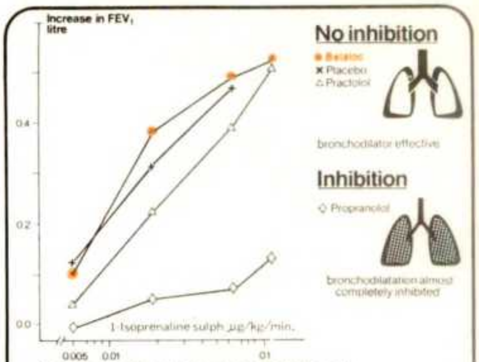

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1 (1975), *Acta pharmacol et toxicol.*, 36, Suppl. V, 39-68 University of Gothenburg, Sweden.

2 Clinical Report (1975), University of Gothenburg, Sweden.

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1. Lancet, 1973, ii, 399 2. Lancet, 1973, ii, 404 3. Amer. Heart J., 1976, *91*, 58
4. Circulation, 1975, 51 & 52, Suppl. II, 147 5. Lancet, 1975, i, 1257 6. Circulation, 1975, 51 & 52, Suppl. II, 199

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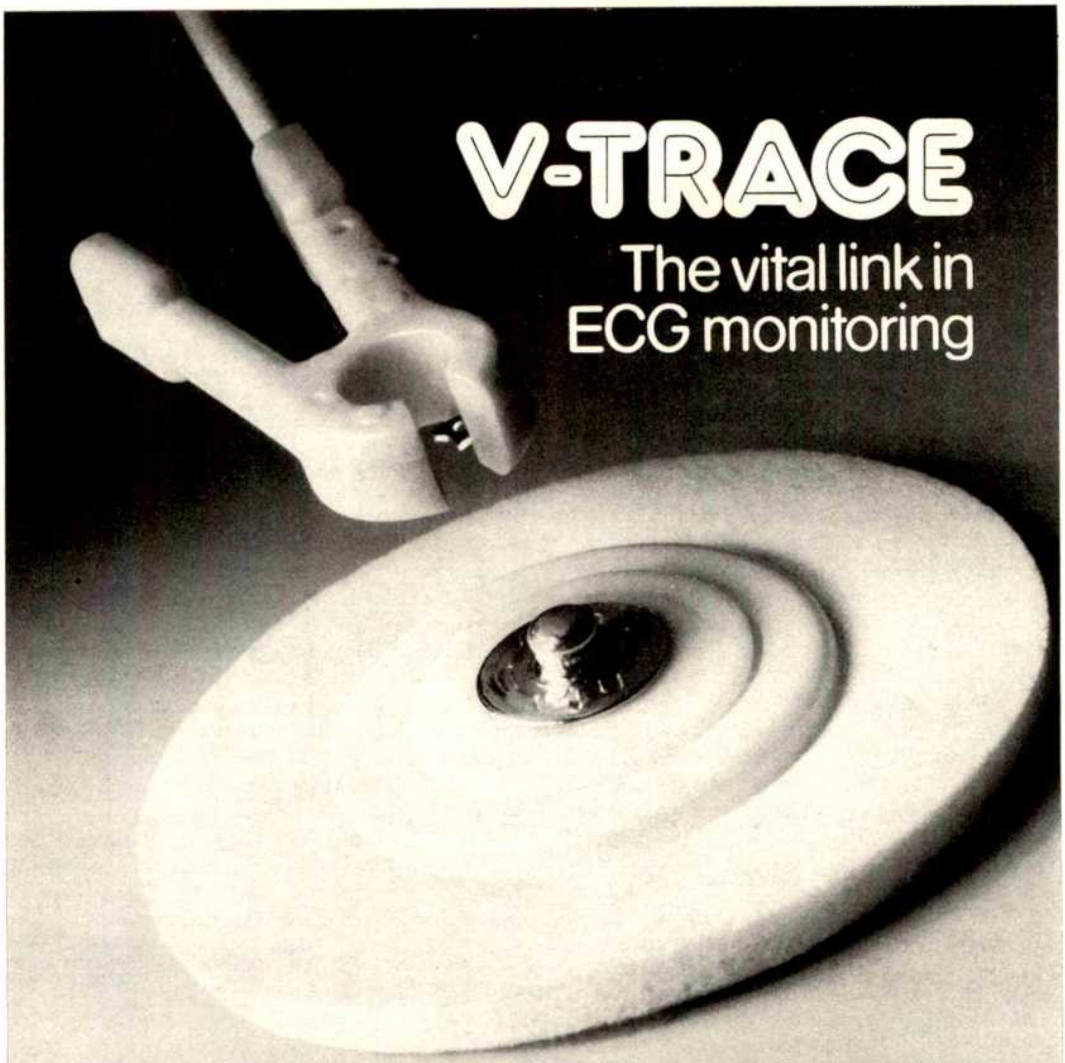

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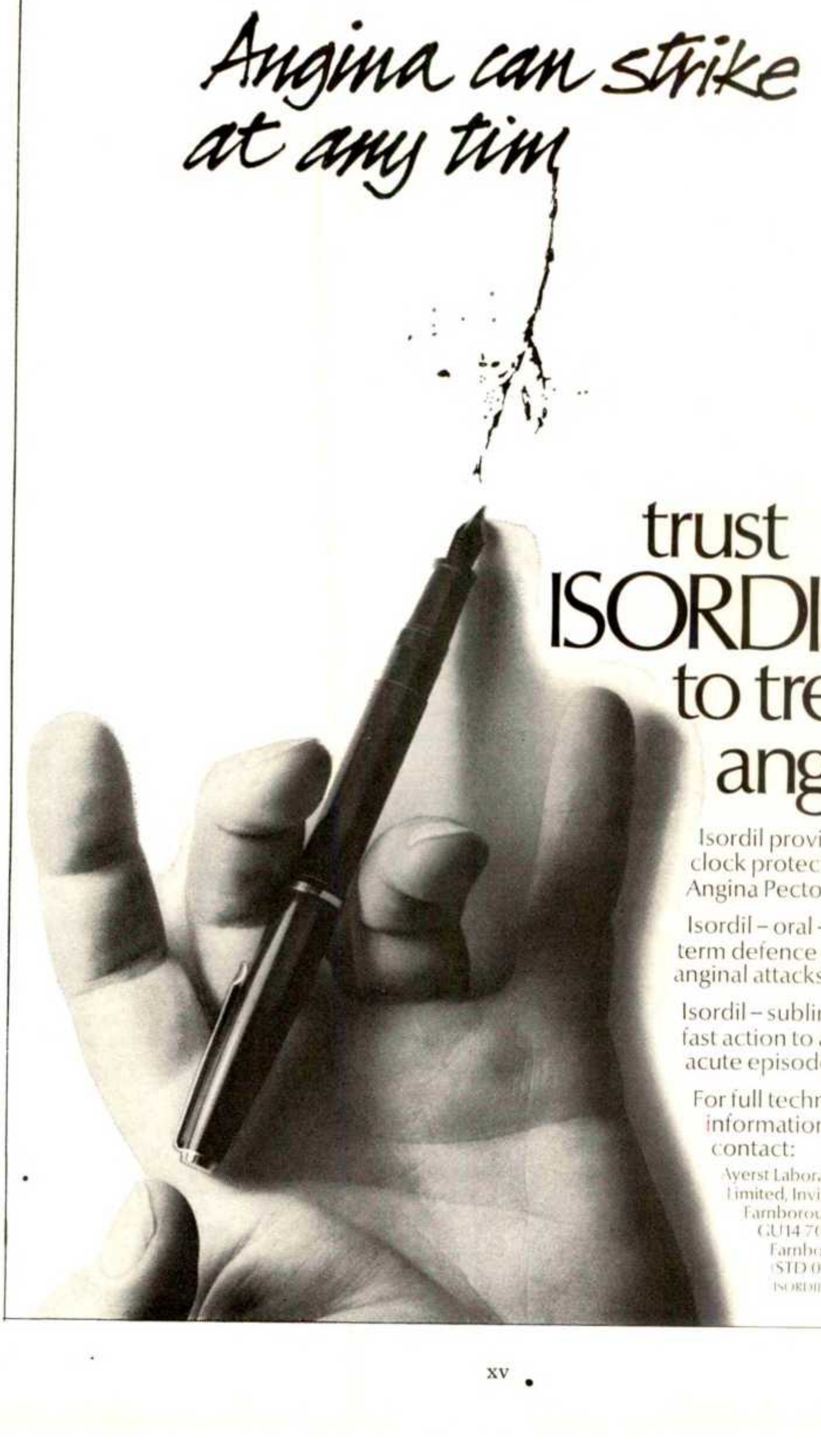

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British Heart Journal, 1976, **38,** 541–548.

Clinical, haemodynamic, and angiographic findings in Löffler's eosinophilic endocarditis

J. A. Bell, B. S. Jenkins, and M. M. Webb-Peploe
From the Cardiac Department, St. Thomas' Hospital, London

Detailed haemodynamic and angiographic findings in Löffler's endocarditis are presented for the first time in a report of 3 cases of this rare disease. In 2 of the cases the right ventricular cavity was obliterated; in one of them this was shown by biopsy to be caused by organized thrombus. In the third case, there was progressive mitral regurgitation.

Since Löffler (1936) described 2 cases of fibrous endocarditis there have been occasional reports of this rare condition. Reinbach (1893) anticipated Löffler's findings with a report of a woman with eosinophilia in whom greyish-white mural thrombus was found on the right ventricular endocardium at necropsy. Brockington and Olsen (1973), in a survey of the published reports, found 87 cases with a post-mortem diagnosis of Löffler's endocarditis; they added 3 further cases. Two other cases, proved at necropsy, have been described (Rasche, Kelsch, and Weaver, 1973; Shepherd *et al.,* 1971).

The relation of Löffler's endocarditis to endomyocardial fibrosis is debated. Davies (1961) clearly distinguished the two on the basis of the systemic involvement and greater incidence of embolic phenomena in Löffler's disease. He noted that the cardiac lesions were similar but that in endomyocardial fibrosis they were usually confined to the inflow tract and rarely involved the middle or outer part of the myocardium. Roberts, Liegler, and Carbone (1969) and Brockington and Olsen (1973) suggest that the myocardial lesion in the two diseases cannot be distinguished histologically. The haemodynamic and angiographic findings in endomyocardial fibrosis are clearly defined (Somers *et al.,* 1968; Shillingford and Somers, 1961; Abrahams, 1962; Fowler and Somers, 1968; Cockshott, 1965). Physiological studies have been reported in only a few cases of Löffler's endocarditis (Roberts *et al.,* 1969; Davies, Deuchar, and Missen, 1965; Lennox, 1948; Clark, Valentine, and Blount, 1956; Nagy *et al.,* 1969; Gardner-Thorpe *et al.,* 1971; Van der Hauwaert, Corbeel, and Maldague, 1965). They suggest that the haemodynamic characteristics of the two diseases are similar.

Though the combination of eosinophilia and unexplained heart failure may suggest the diagnosis, Löffler's endocarditis is rare and is seldom diagnosed before necropsy. We present comprehensive haemodynamic data in 3 cases in which the diagnosis was made in life.

Case reports

Case 1

A 56-year-old white man was seen in 1971 with symptoms of peptic ulceration. He had served in North Africa during the second world war and had had no illness at that time. He reported several attacks of soreness and swelling of the tongue relieved by chlorpheniramine. A routine blood test showed an eosinophilia (white blood cells $17{\cdot}9 \times 10^9/l$, eosinophils 31%). Stool examination for parasites and serological tests for trichinella and toxocara were negative.

In mid-1972 he noted dyspnoea on exertion and an episodic irritating skin rash. Clinical examination showed a slightly raised jugular venous pressure, ankle oedema, a soft systolic murmur in the mitral area, and an enlarged liver. The spleen was not palpable. Abnormal results of investigations included a white blood cell count of $9{\cdot}9 \times 10^9/l$ (eosinophils 25%) and the following immunoglobulin levels: IgG 16·30 g/l, IgA 1·06 g/l, and IgM 9·04 g/l. Protein electrophoresis showed a paraprotein band. Cold agglutinins were detected, and were found to be mixed IgG and IgM complexes. The Rose-Waaler titre was positive in a

Received 21 November 1975.

TABLE *Cardiac catheterization data in 3 cases of Löffler's endocarditis*

	Case 1	*Case 2*	*Case 3*
Body surface area (m^2)	1·84	1·77	1·56
Pressures (mmHg above sternal angle)			
RA	12/5 (mean 10)	a 13; x 4; v 11; y 4 (mean 8)	a 13; x 1; v 8; y 0 (mean 5)
RV	12/5	10/2	60/2–15
PA	12/5 (mean 10)	10/3 (mean 6)	60/30 (mean 37)
LA	a 6; x 2; v 5; y 3 (mean 5)	a 4; x 0; v 8; y 1 (mean 4)	a 18; x 17; v 48; y 17 (mean 26)
LV	95/7–12	95/0	105/0–18
Ao	95/75	95/60	105/74
Telco micromanometer data			
Sinus beat: max dP/dt (mmHg s^{-1})	1122	1620	1353
KVmax (s^{-1})	65	130	84
Post-ectopic beat: max dP/dt (mmHg s^{-1})	1440	2280	1535
KVmax (s^{-1})	100	380	93
Cardiac index (l/min per m^2)	2·2	2·2	2·8
Angiographic volumes (ml per m^2)			
EDV	59	98	173
ESV	26	42	87
SV	33	56	86
Ejection fraction (EDV s^{-1})	0·55	0·57	0·50
Normalized ejection rate (EDV s^{-1})	3·0	2·2	2·2
Angiography			
Left ventricular angiogram	Slightly thick-walled LV with smooth deformed apex; grade 1/4 early systolic mitral regurgitation	Normal	Slightly enlarged LV contracts well; grade 3/4 mitral regurgitation with left atrial systolic expansion
Aortogram	—	—	Grade 1/4 aortic regurgitation
Right ventricular angiogram	Gross tricuspid and pulmonary regurgitation with almost complete obliteration of RV apex and body, leaving only infundibulum opacified	Similar to Case 1	—
Coronary angiogram	Normal	Normal	50% narrowing of left anterior descending artery distal to first diagonal

Conversion factors from Traditional to SI Units: 1mmHg≈0·133 kPa.

dilution of 1:256. The latex titre was less than 1:20. No antinuclear antibodies were present. The serum complement level was normal. Chest *x*-ray examination, electrocardiogram, liver and lung scans, peripheral phlebograms, and 24-hour urinary 5-hydroxyindole-acetic acid (5-HIAA) excretion were normal. An echocardiogram showed a normal mitral valve but paradoxical septal motion; neither the right ventricle nor the tricuspid valve was identified. A bone marrow aspirate contained an increased number of eosinophils and their precursors. A needle liver biopsy specimen was infiltrated with histiocytes, lymphocytes, and eosinophils. A definite diagnosis was not made.

Over the next two years increasing breathlessness, fatigue, and ankle swelling developed. Despite increasing doses of diuretics, the heart increased in size and there was a progressive rise in jugular venous pressure, with prominent v wave. The eosinophilia persisted and nodal rhythm developed. In January 1974 cardiac catheterization (Table and Fig. 1) showed identical pressures throughout the right heart chambers. Right ventricular angiography confirmed free tricuspid and pulmonary regurgitation with extensive obliteration of the right ventricular cavity (Fig. 2). Left ventricular endomyocardial biopsy showed focal areas of fibrosis in the myocardium, appearing in one area to extend to the endocardial surface; no eosinophils were seen. A diagnosis of Löffler's endocarditis was made and treatment started with corticosteroids, azathioprine, and anticoagulants. At the most recent follow up the patient was improved subjectively but the physical signs remained unchanged.

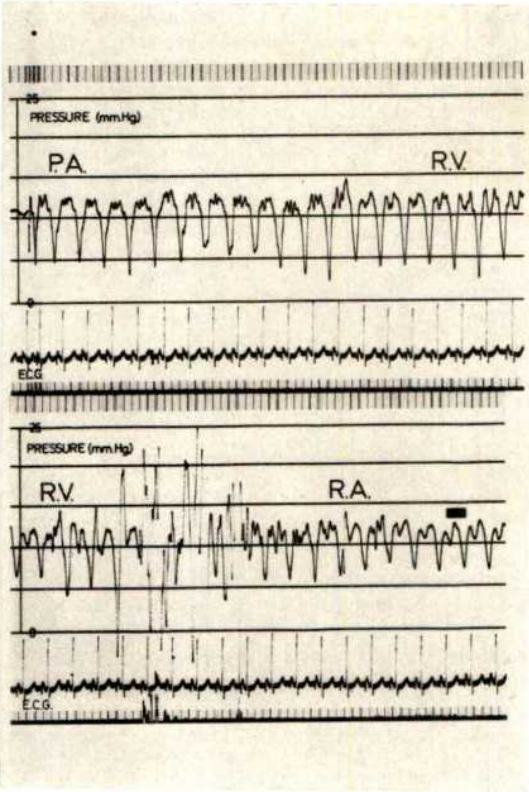

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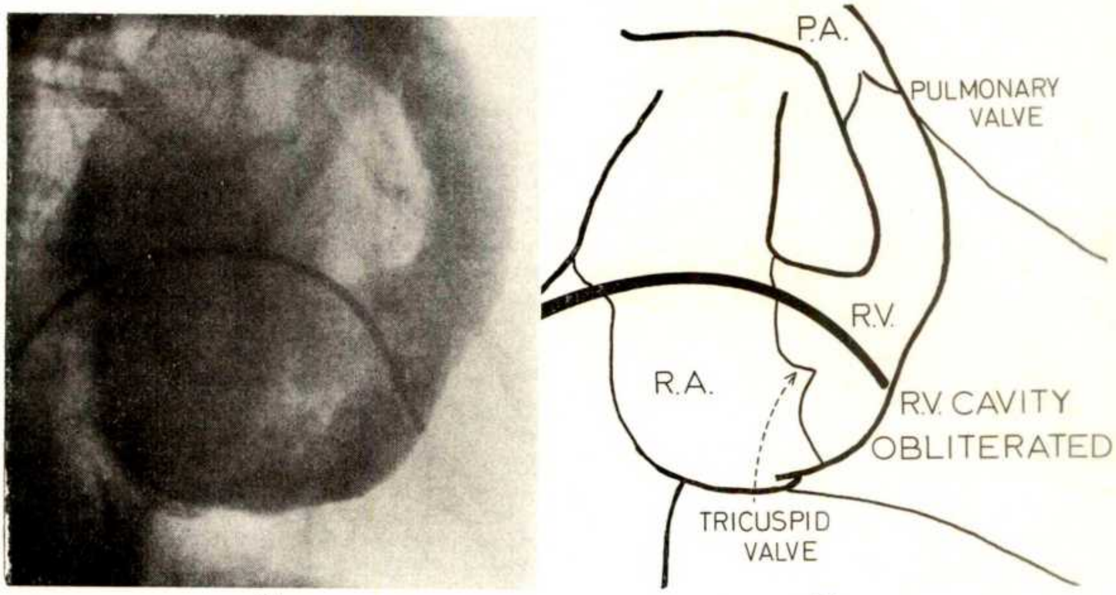
FIG. 1 *Right heart pressures: withdrawal record (Case 1)*

Case 2

The patient, a 48-year-old white man, had spent the first 34 years of his life in India. At the age of 24 he had malaria. He remained well until January 1974 when he noted ankle swelling and breathlessness. He was not orthopnoeic. Findings at another hospital were a raised jugular venous pressure, peripheral oedema, and hepatosplenomegaly. The eosinophil count was high (white blood cells $21 \cdot 7 \times 10^9$/l, eosinophils 74%), and a bone marrow aspirate showed an excess of eosinophils and their precursors. He was treated with diuretics and transferred to this hospital with a provisional diagnosis of lymphoma or eosinophilic leukaemia.

On admission the jugular venous pressure was raised 15 cm, with equal a and v waves. The right ventricular impulse was palpable and in the tricuspid area there was a pansystolic murmur, a loud third sound, and a short diastolic murmur. Stool examination for ova and parasites was negative and serological tests were also negative. Chest *x*-ray film, electrocardiogram, lung scan, and 24-hour urinary 5-HIAA excretion were normal. An echocardiogram showed a normal mitral valve but paradoxical septal motion; the tricuspid valve was not



(A) (B)

FIG. 2 *(A) Right ventricular cineangiogram: right anterior oblique projection (Case 1). (B) Line drawing of same frame*

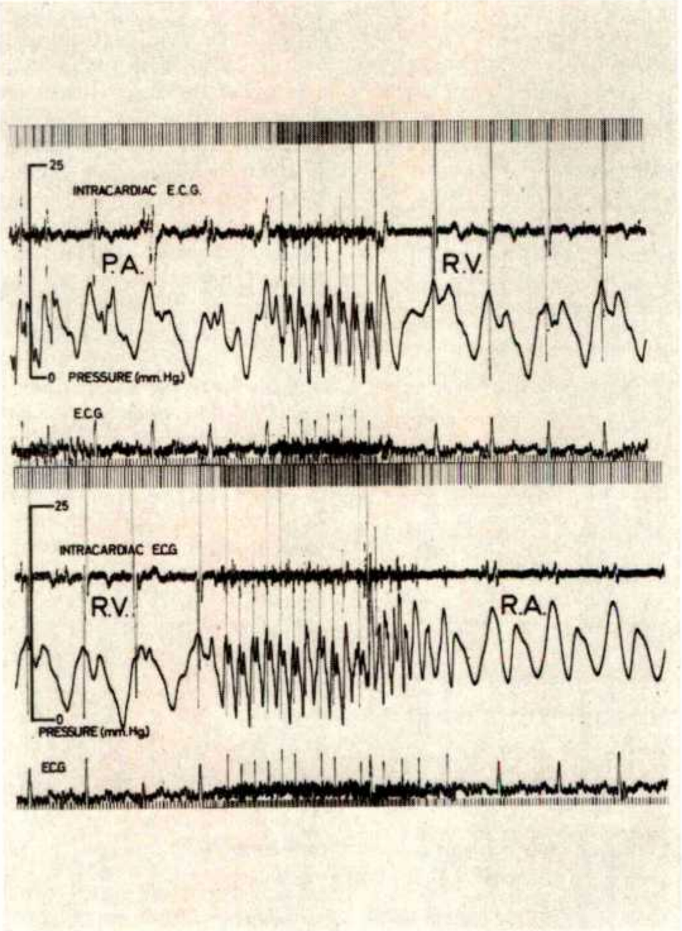


FIG. 3 *Right heart pressures: withdrawal record (Case 2)*

seen. Needle liver biopsy showed infiltration of some portal tracts with neutrophils and eosinophils.

Cardiac catheterization (Table and Fig. 3) showed severe tricuspid regurgitation and mild tricuspid stenosis, and the right ventricular cavity was almost totally obliterated (Fig. 4). Right ventricular endomyocardial biopsy showed only organized thrombus. A focal area of fibrosis was found in the left ventricular myocardium; the myofibrils appeared normal apart from myocytolysis in the fibrotic area; no eosinophils were seen.

A clinical diagnosis of Löffler's endocarditis was made and treatment with corticosteroids, azathioprine, and anticoagulants started.

The patient died from cardiac failure after eight months. Necropsy confirmed obliteration of the right ventricular cavity. There were firm adhesions between the tricuspid valve cusps and the right ventricular endocardium; the valve itself was narrowed to a 2-cm orifice. There were a few small vegetations on the opposing surfaces of the mitral valve leaflets.

Case 3

The patient, a 47-year-old white man, presented in 1969 with a three-week history of abdominal pain. The only time he had spent abroad was during the second world war, when he served in the Middle East. He had splenomegaly and a high eosinophil count (white blood cells $17{\cdot}4\times10^9$/l, eosinophils 64%). Investigations for parasites were negative, bone marrow aspirate showed an increase of neutrophil and eosinophil myelocytes and promyelocytes, and a needle liver biopsy showed infiltration of occasional portal tracts by lymphocytes and a few eosinophils. Atypical chronic myeloid or eosinophil

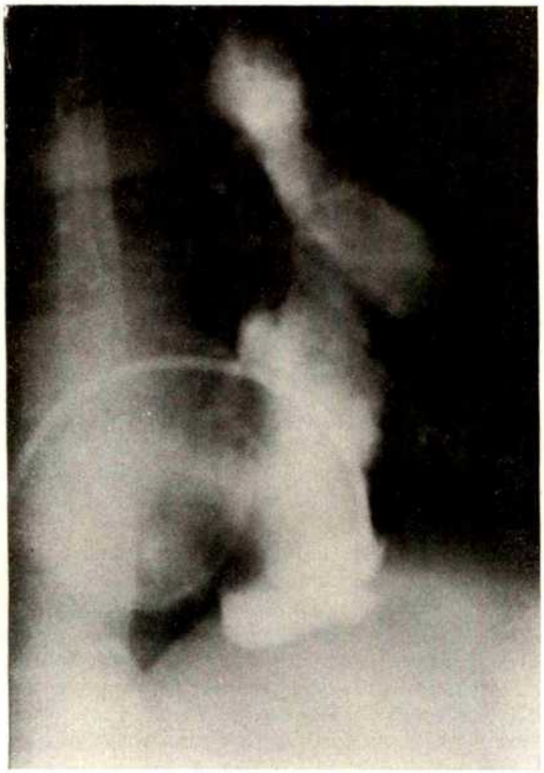


FIG. 4 *Right ventricular angiocardiogram: right anterior oblique (Case 2). This shows obliteration of most of body and apex of right ventricle*

leukaemia was diagnosed and treatment with busulphan and prednisone begun.

A few months later, when he was readmitted with further splenic pain, an apical pansystolic murmur was noted for the first time. The heart was of normal size on chest *x*-ray examination and an electrocardiogram showed sinus rhythm with a mean frontal QRS vector of 0°. The eosinophilia was less. Treatment was started with azathioprine, chlorpheniramine, and diuretics in addition to corticosteroids. During the next two years the patient was admitted with pneumonia on one occasion and a retinal artery branch embolus on another. In mid-1971 he was readmitted in heart failure with signs of severe mitral regurgitation. There was clinical and radiographic evidence of an enlarged heart and pulmonary venous congestion. The electrocardiogram now showed a mean frontal QRS vector of –60°, left atrial hypertrophy, and a T-wave abnormality. An echocardiogram showed an enlarged left atrial dimension (4·9 cm) and a normal mitral valve.

Initially he responded to conventional treatment of heart failure, but in August 1973, after a progressive worsening of his symptoms, cardiac catheterization was performed. Severe mitral regurgitation, mild aortic regurgitation, a 50 per cent stenosis of the left anterior descending coronary artery, and moderate impairment of left ventricular function was found (Table). Endomyocardial biopsy was unsuccessful.

Mitral annuloplasty and a left anterior descending bypass graft procedure were performed at the National Heart Hospital (Mr. Donald Ross). The operation was technically difficult because of excessive friability of all the tissues. The mitral valve leaflets were floppy, with attenuated chordae, and the mitral ring was dilated. The histology of the rectus abdominis muscle, aorta, and internal mammary artery was normal. Myocardial biopsy was not done. The diagnosis of Löffler's endocarditis was thus not proved, but seemed the most likely.

Six months after operation the patient had an increased exercise tolerance and no orthopnoea.

Discussion

Cases with similar clinical findings to those of Löffler's endocarditis (Brockington and Olsen, 1973; Rasche *et al.*, 1973) have been reported as cases of eosinophilic leukaemia (Bentley *et al.*, 1961), disseminated eosinophilic collagen disease (Engfeldt and Zetterström, 1956), fibroma of the right ventricle (Van der Hauwaert *et al.*, 1965), Löffler's eosinophilic endocarditis (Gardner-Thorpe *et al.*, 1971), and endocarditis parietalis fibroplastica (Nagy *et al.*, 1969; Jennings and Pengelly, 1968). Löffler's endocarditis is one of the rarest cardiomyopathies and over the decade 1960 to 1970 only one case was seen at the clinical cardiology unit at the Royal Postgraduate Medical School, London. During that period 246 cases of hypertrophic and congestive cardiomyopathies were seen (Oakley, 1973).

In the face of the semantic problems diagnostic criteria are difficult to establish. An eosinophilia, often intense, with counts as high as $126 \times 10^9/l$ (Rasche *et al.*, 1973), is an essential feature. The cause of the eosinophilia may not be apparent but the characteristic cardiac findings are described in association with the eosinophilia of parasitic infestation and other allergies, malignant disease, and polyarteritis. Odeberg (1965) and Bousser (1957) have doubted the existence of true eosinophil leukaemia and comment on the maturity of the eosinophils in the bone marrow.

A high eosinophil count was a feature of all the cases described here. No cause for the eosinophilia was found in our Cases 2 and 3. In Case 1 angioneurotic oedema and the rash suggest an allergy. The raised plasma IgM, the positive Rose-Waaler test, and the presence of cold agglutinins supported this, but the allergen remains unidentified.

Löffler's disease predominantly affects men. Though the clinical presentation is variable, progressive heart failure, a febrile course, and multiple systemic emboli are said to be characteristic (Davies, 1960). The cardiac lesion at the onset may be occult but later dominates the clinical picture and determines the outcome. Non-specific or incidental symptoms may lead to the discovery of eosinophilia as in Cases 1 and 3. Apical systolic murmurs, common in reported cases of Löffler's endocarditis, were present in 20 of the 40 cases reviewed by Brink and Weber (1963). Conduction disturbances were seen in 19 of the 65 cases reviewed by Raizner, Silverman, and Waters (1972). Bundle-branch block and intraventricular conduction delays were most frequent, not surprisingly in view of the subendocardial pathological lesion. Systemic emboli occur commonly and are probably responsible for the frequent association with neurological disease (Gardner-Thorpe *et al.*, 1971). Embolism may be the basis for the renal impairment reported in some cases.

Pathologically, hyalinized fibrous endocarditis, subendocardial necrosis or fibrosis or both, plus the presence of mural thrombi are described (Brockington and Olsen, 1973). Extensive thrombosis, eosinophilic infiltration, periarteritis, and endarteritis of small vessels, as well as involvement of the whole thickness of the ventricular wall are reported as important distinctive features of Löffler's endocarditis (Davies, 1960). In the 90 cases reviewed by Brockington and Olsen (1973), 46 had biventricular endomyocardial lesions, 35 left ventricular lesions, and 9 only right ventricular lesion. The left ventricular endomyocardial biopsy specimens in Cases 1 and 2 were difficult to assess because of their small size and difficulty in orientation. Nevertheless, they were unequivocally abnormal and the histological features were compatible with a diagnosis of Löffler's endocarditis. Several attempts had to be made in each case to obtain biopsy material, and the failure to obtain a specimen showing hyaline thickening of the endocardium may be a result of the nature of the lesion. Endomyocardial biopsy may also be difficult in endomyocardial fibrosis as the bioptome tends to slide over the smooth fibrous endocardium (Somers *et al.*, 1971). Right ventricular biopsies in Case 2 showed organized thrombus. No biopsy specimen was obtained in Case 3, but the excessive myocardial friability noted at operation suggests myocardial involvement. Valvular lesions are described in more than 20 per cent of the published cases: the tricuspid and mitral valves are most commonly affected. Postmortem studies indicate two main reasons for mitral regurgitation. There may be warty deposits or friable vegetations on the mitral valve leaflets (Brockington and Olsen, 1973) or, more commonly, one of the mitral valve leaflets, usually the posterior, is tethered by the fibrous endocardium (Rasche *et al.*, 1973; Roberts *et al.*, 1969). Eosinophilic and lymphocytic infiltration of liver and spleen have been described in necropsy material in most cases and were present in liver tissue in our cases.

The cardiac lesions in Löffler's endocarditis have many histological features in common with endomyocardial fibrosis. The relative incidence of left and right ventricular lesions in Löffler's endocarditis is the same as in endomyocardial fibrosis (Shaper, Hutt, and Coles, 1968), which often presents with severe right heart failure. It is characteristic of severe right-sided endomyocardial fibrosis that identical pressures are recorded throughout the right heart, and the value of the intracardiac electrocardiogram in locating the tricuspid and pulmonary valves in this disease has been reported (Emslie-Smith and Somers, 1968). Our cases show for the first time that both the haemodynamic and angiographic findings in Löffler's endocarditis can mimic those described in endomyocardial fibrosis (Somers *et al.*, 1968; Cockshott, 1965). A variant of endomyocardial fibrosis presenting as mitral regurgitation of varying severity has been described (Fowler and Somers, 1968). Shillingford and Somers (1961) made haemodynamic observations in 15 cases and found mitral regurgitation in 12, which was severe in 7; the cardiac lesion in our Case 3 is very like that seen in this type of endomyocardial fibrosis. Löffler's endocarditis is an uncommon multisystem disease which has been reported from various parts of the world whereas endomyocardial fibrosis primarily affects the heart and has a very well-defined geographical distribution. While the pathogenetic mechanisms which lead to the cardiac lesions may have features in common, perhaps reflecting a restricted spectrum of endocardial responses to disease, the two diseases should not be regarded as variants of a single entity.

Cases 1 and 2 are clearly Löffler's endocarditis and Case 3 almost certainly so on the grounds of the systemic disease with obvious eosinophilia together with a compatible cardiac lesion. Cases 1 and 2 show remarkable similarities: one presented with and the other developed severe right heart failure and tricuspid incompetence; in neither was there clinical evidence of left heart involvement. Cardiac catheterization in both cases showed normal left heart pressures. In both, right ventricular contraction produced no measurable effect on the right-sided pressures and hence right heart work, though normal cardiac outputs were maintained. The right ventricular angiograms were similar to those reported by Gardner-Thorpe *et al.* (1971), and Van der Hauwaert *et al.* (1965). In Case 1 the deformed left ventricular apex and the early systolic mitral regurgitation suggest left-sided involvement. In Case 2, though the right ventricle was equally affected, left ventricular function was normal. The dominant picture in both cases was a severe right-sided obliterative cardiomyopathy. We should have paid more attention to the echocardiogram in these two cases. Paradoxical septal motion in right heart failure implies right ventricular volume overload, and in such patients there should be no difficulty in identifying both the right ventricle and the tricuspid valve (Popp *et al.,* 1969). Neither could be identified and the extensive obliteration of the right ventricular cavity in both cases provides a ready explanation for this.

The haemodynamic findings in Case 3 were very different from those in the other two. Clinically there was mitral regurgitation of increasing severity. A rheumatic aetiology seemed unlikely in view of the normal mitral echocardiogram. Though ischaemic heart disease could not be excluded, a cardiomyopathy was thought to be the most likely cause. Cardiac catheterization confirmed severe mitral regurgitation. Coronary arteriography showed only moderate stenosis of the left anterior descending coronary artery. An ejection fraction of 0·5 and a low KVmax with impaired postectopic response indicated poor left ventricular function. There was no angiographic evidence of endocardial thickening or mural thrombus in the left ventricle. The mitral regurgitation was more akin to that seen in congestive cardiomyopathies with a dilated mitral ring, but in addition the mitral leaflets were found at operation to contain redundant tissue ('floppy valve'). Right ventricular angiography was not done. The raised right-sided pressures were probably secondary to the raised left atrial pressure, rather than the result of a constrictive process.

There is little information on left ventricular function in Löffler's endocarditis. It is not certain whether the two patients described by Davies *et al.* (1965) had endomyocardial fibrosis or Löffler's endocarditis. Both had raised left atrial pressures secondary to endocardial restriction and resembled mitral stenosis. Others have noted raised pulmonary artery wedge pressures (Roberts *et al.,* 1969; Clark *et al.,* 1956), but mitral regurgitation was present in these patients. Undoubtedly left ventricular disease is common without clinical evidence of impaired filling. The left ventricular biopsies in Cases 1 and 2 both showed fibrosis and it is possible that in some cases high left-sided filling pressures are the result of a restriction of left ventricular filling resulting from fibrosis. Despite considerable pathological evidence of left ventricular disease (Brockington and Olsen, 1973), the lack of clinical evidence for this in most cases remains unexplained. In Case 1 left ventricular dysfunction was seen at cardiac catheterization. The predominant haemodynamic involvement of the right ventricle in this disease may protect the left ventricle to the extent that its dysfunction does not become clinically detectable.

There is no established specific therapy. Congestive heart failure is treated conventionally with digoxin and diuretics. Our patients were given anticoagulants in view of the high incidence of systemic emboli in previously reported cases. Azathioprine and prednisone were given in all three cases. There was a progressive reduction in the size of the spleen and in the eosinophil count, but there was no evidence of improvement or reduced rate of progression of the cardiac lesion. One patient died within a year of the development of cardiac symptoms. A single case of Löffler's endocarditis has been reported in which corticosteroids produced temporary beneficial results but no improvement was noted in others (Nagy *et al.,* 1969; Jennings and Pengelly, 1968).

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Vectorcardiographic study of aberrant conduction[1]

Anterior displacement of QRS: another form of intraventricular block

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Aberrant ventricular conduction was induced in 44 subjects by introduction of atrial premature beats through a transvenous catheter-electrode. Multiple patterns of aberrant ventricular conduction were obtained in 32 patients and, in the whole group, 116 different configurations were recorded. Of these, 104 showed a classical pattern of mono- or biventricular conduction disturbance. The pattern frequencies were as follows: right bundle-branch block, 28; left anterior hemiblock combined with right bundle-branch block, 21; left anterior hemiblock, 17; left posterior hemiblock combined with right bundle-branch block, 12; left posterior hemiblock, 10; complete left bundle-branch block, 10; and incomplete left bundle-branch block, 6. The remaining 12 configurations could not be classified into the usual categories of intraventricular blocks. In 7 of them, the alterations only consisted of trivial modifications of the QRS contour. In the other 5 instances, aberrant conduction manifested itself by a conspicuous anterior displacement of the QRS loop, with increased duration of anterior forces. The latter observation is worthy of notice, as it indicates that, in the differential diagnosis of the vectorcardiographic pattern characterized by prominent anterior forces, conduction disturbances should be considered a possible aetiological factor in addition to right ventricular hypertrophy, and true posterior wall myocardial infarction.

Introduction of atrial premature beats through a transvenous catheter-electrode has been used in human beings in order to produce aberrant ventricular conduction (Cohen *et al.*, 1968; Kulbertus *et al.*, 1971; Kulbertus, 1972; Wu *et al.*, 1974). The data from these experiments enabled the authors to describe the vectorcardiographic features of different conduction defects in their pure intermittent form (Cohen *et al.*, 1968; Kulbertus, 1972) and to investigate their influence on various pathological vectorcardiographic manifestations (Cohen *et al.*, 1968; Kulbertus *et al.*, 1971; Kulbertus, 1972).

The present report is concerned with the observations made in 44 subjects by delivering premature atrial stimuli throughout the diastolic period. Attention will be drawn towards an unusual variety of conduction disturbance, with conspicuous anterior displacement of the QRS.

Patients and methods

Studies were made on 44 patients (30 men and 14 women) with normal sinus rhythm whose ages ranged from 14 to 71, with an average of 51. Among the 44 investigated, 2 were normal subjects. Eight patients had arterial hypertension, 3 chronic airways obstruction, 13 peripheral vascular disease, and 14 coronary heart disease. Eleven of the 14 with coronary heart disease had a history of previous myocardial infarction diagnosed on the basis of suggestive clinical signs, with typical electrocardiographic abnormalities at the time of the acute episode. The remaining subjects had valvular lesions (12 cases), congenital malformations (2 cases), or hypertrophic obstructive cardiomyopathy (1 case).

The classification based on the control electrocardiographic tracing included 10 subjects with normal electrocardiograms, 11 patients with residua of myocardial infarction, 12 patients with left anterior hemiblock (once combined with right

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TABLE *Patterns of aberrant conduction induced by atrial extrastimuli in 44 patients*

Case No.	*Age (yr)*	*Left anterior hemiblock*	*Left posterior hemiblock*	*Left bundle-branch block*		*Complete right bundle-branch block**		*Left anterior hemiblock and complete right bundle-branch block**		*Left posterior hemiblock and complete right bundle-branch block**		*Unclassified patterns*	
				Complete	*In-complete*	*A*	*B*	*A*	*B*	*A*	*B*	*Anterior shift*	*Others*
Normal electrocardiograms													
1	47	3					3		1				1
2	48							1					1
3	52						2						
4	22		1	1									
5	14						2					1	
6	59		3	1						1			
7	60						1		1		1	1	1
8	53						1					1	
9	45					1	2						
10	48								1				1
Left anterior hemiblock													
11	70	1							1				
12	63							1					
13	67	1				1							
14	59	1											
15 (+RBBB)	65							1		1			
16	66	2		1									1
17	55							1				Normal electrocardiogram	
18	58	1		1	1			1	1				
19	63	2			1								
20	62+A† inf.											1	1
21	41					1		1	1				
22	31					2							
Left ventricular hypertrophy													
23	36									2			
24	39										1		
25	33							1					
26	35		2								1		
27	35		1	2		2		1	1	1			
Right ventricular hypertrophy													
28	59					1	1						
29	34		1							1			
30	36						1						
31	52							1					
32	44						1						
33	46				1						1		
Myocardial infarction													
34	67 (PD)‡	1											
35	71 (PD)	1											
36	60 (PD)		1				1						
37	56 (PD)		1		1						1	1	
38	53 (PD)	1			1		1		2				
39	68 (PD)	2		1	1	1			1				1
40	54 (PD)	1											
41	45(A+PD)			1		1				1			
42	48 (A)			1									
43	70 (A)			1		1			1				
44	54 (A)						1		1				
Total (patients)		12	7	9	6	9	12	9	11	6	5	5	7
(morphologies)		17	10	10	6	11	17	9	12	7	5	5	7
				16		28		21		12		12 +1N	

*See text for description of types A and B.

†A: anterior.

‡PD: posterodiaphragmatic.

The location of the infarcted area was determined on the basis of the electrocardiographic changes at the time of the acute episode.

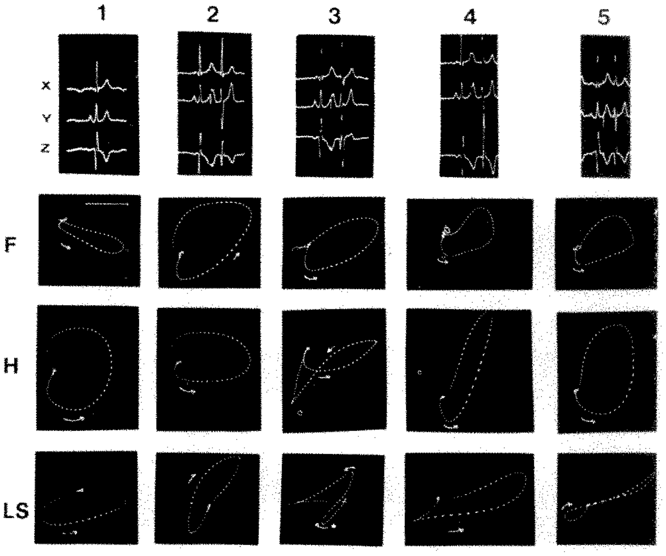

FIG. 1 *Tracings obtained from man aged 47, with peripheral vascular disease and normal resting electrocardiogram. First picture (1) shows control tracing; other four, various aberrantly conducted beats; 2: left anterior hemiblock; 3: left anterior hemiblock with right bundle-branch block; 4 and 5: two other variants of left anterior hemiblock, with possibly, some degree of incomplete left bundle-branch block. The loops are interrupted every 1·25 ms. Calibration: 0·5 mV.*

bundle-branch block), 6 patients with right ventricular hypertrophy, and 5 with left ventricular hypertrophy.

All these patients were studied during cardiac catheterization or during investigation for coronary artery disease. Informed consent was obtained in each case.

An electrode-catheter was pushed through the brachial vein into the right atrium. By means of an R wave coupled pulse generator (Medtronic Model 5837), atrial stimuli were delivered throughout the diastolic period at 5- to 10-ms intervals. Spatial vectorcardiograms were recorded using the McFee-Parungao axial system (1961) by means of a Hewlett-Packard 1520 A vectorcardiograph. The X, Y, and Z scalar leads were recorded on a magnetic tape (HP Instrumentation recorder 3960 A) at a speed of 19 cm (7½ in) per min. They were later reproduced in linear and loop modes on an oscilloscope and photographed by means of a Polaroid camera.

The diagnosis of complete or incomplete left and right bundle-branch block was made according to currently agreed criteria (Chou, Helm, and Kaplan, 1974). For the purposes of description and in the presence of right bundle-branch block, a distinction was made between types A and B (Kulbertus, Collignon, and Humblet, 1970a), type A being characterized by a counterclockwise horizontal plane loop and type B by an entirely anterior and clockwise rotated loop in the transverse projection.

The existence of left anterior hemiblock was recognized by means of previously described morphological characteristics (Kulbertus, Collignon, and Humblet, 1970b; Benchimol, Barreto, and Pedraza, 1971; Chou *et al.*, 1974). Left posterior hemiblock was diagnosed only by comparison with the control tracing. It was thought to be present when the following changes occurred: (1) inferior axis shift (whatever its importance); (2) displacement of the initial forces towards the left, anterior and superior octant; and (3) displacement of the midtemporal and late vectors towards the right inferior, and posterior octant (Rosenbaum, Elizari, and Lazzari, 1970; Kulbertus, 1972). Finally, the diagnosis of anterior displacement of QRS was made when the portion of the horizontal loop located anterior to the X axis exceeded 70 per cent of the total loop area and when the duration of anterior forces was greater than 50 ms (Chou *et al.*, 1974).

Results

Multiple patterns of aberrant conduction were obtained in 32 out of the 44 patients. On the whole,

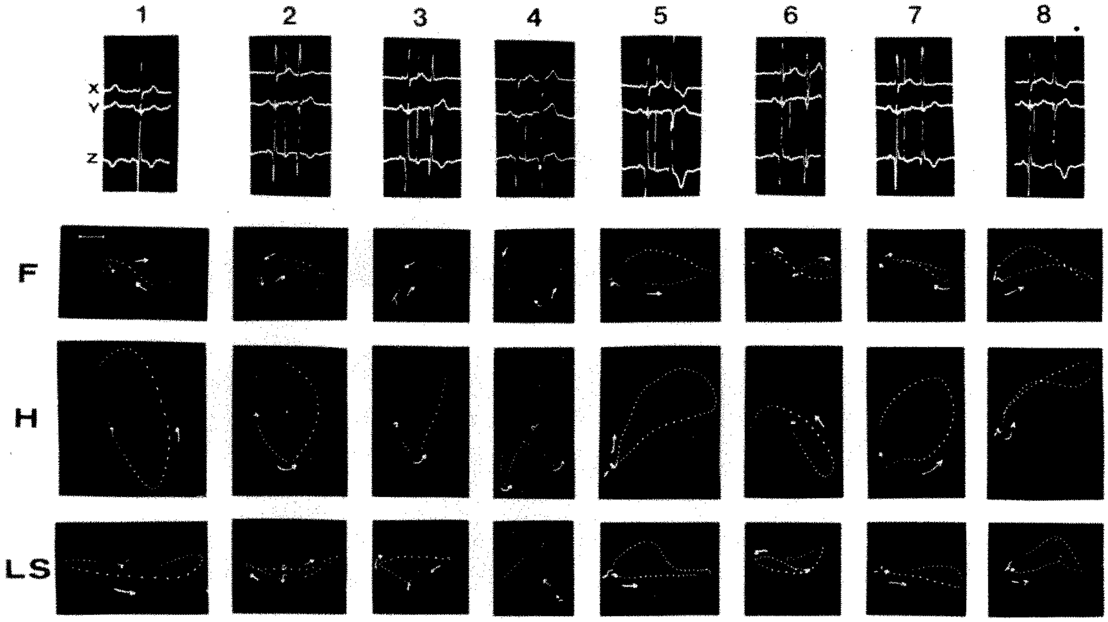

FIG. 2 *Tracings obtained from woman aged 68 with history of previous inferior infarct (10 years before). 1: control tracing. Sequelae of previous infarct are inconspicuous; 2 and 3: left anterior hemiblock with signs of concomitant inferior infarct; 4: left anterior hemiblock with right bundle-branch block and signs of inferior infarct; 5: complete left bundle-branch block; 6: complete right bundle-branch block; 7: slight modification of QRS with attraction of both efferent and afferent limbs towards left posterior quadrant and development of a concavity from anterior occurring from 15 to 30 ms (slight degree of incomplete left bundle-branch block ?); 8: posterior displacement of efferent limb with clockwise rotation of initial portion of QRS compatible with incomplete left bundle-branch block. Loops are interrupted every 1·25 ms. Calibration: 0·5 mV.*

116 different configurations were produced. Of these, 104 showed the typical morphology of one of the classical categories of mono- or bilateral conduction disturbances. The remaining 12, though obviously different in shape from the control vectorcardiogram, could not be readily classified into the usual categories of intraventricular conduction defects. The results from each case are presented in the Table, together with the pattern frequencies. Illustrative examples are shown in Fig. 1, 2, 3, and 4.

Left anterior hemiblock

In 4 cases, several morphologies compatible with the diagnosis of left anterior hemiblock were induced in the same patient (Fig. 1). They differed from one another by the degree of axis shift, the direction of the initial forces, and small variations of the QRS morphology and/or duration.

Twelve patients with pre-existing typical left anterior hemiblock were subjects in this experiment. Their control tracings all showed initial forces pointing anteriorly, inferiorly, and to the right. In one of these cases, the ventricular complexes that followed atrial premature stimulation resumed a normal QRS configuration. A pattern of isolated right bundle-branch block developed in three other instances, whereas 8 patients showed aberrantly conducted beats with left anterior hemiblock and right bundle-branch block (5 types A and 3 types B). Finally, in 6 of these cases, a variant of the left anterior hemiblock morphology was induced; the variations, though small, consistently showed the same features, i.e. a trivial QRS prolongation with widening of the frontal plane loop and leftward shift of the initial forces (Kulbertus, 1975).

Left posterior hemiblock

In 7 cases, the atrial premature beats were followed by ventricular complexes which, by comparison with the control tracings, were considered as examples of left posterior hemiblock. Details of their morphology have been reported previously (Kulbertus, 1972).

It is worth noting that the frontal maximal vector, if it consistently showed a slight inferior and rightward axis shift, was located only once further than +90°. The portion of QRS located to the right of the Y axis was greater than 25 per cent in 3 cases, and equal to 50 per cent in the remaining 4 cases.

The horizontal maximal vector was also slightly deviated posteriorly and to the right, but was located further than –90° in only 3 cases. The portion of the horizontal loop inscribed to the right of the Z axis did not exceed 25 to 30 per cent.

Left bundle-branch block (complete or incomplete)

A pattern of complete left bundle-branch block was obtained in 9 patients. Six others developed aberrantly conducted beats characterized, in the horizontal plane, by a centrifugal limb running backward in a clockwise fashion. Considered in isolation, such complexes might probably have been taken for cases of anterior infarction; however, in the present experimental procedure, the most probable diagnosis was that of incomplete left bundle-branch block (Chou *et al.*, 1974: Fig. 2, col. 8). Three patients in this group had a posterodiaphragmatic infarction. It is worth noting that the evidence for necrosis nearly disappeared in those subjects, when the pattern of incomplete left bundle-branch block developed.

Right bundle-branch block and its associations with left anterior and posterior hemiblock

Isolated right bundle-branch block was the most common conduction disturbance observed after atrial premature stimulation (19 cases). On the whole, the horizontal plane loop was more frequently rotated clockwise than counterclockwise, especially in subjects with normal control electrocardiograms. In 2 patients, both right bundle-branch block patterns could be obtained during the same experiment.

Combined right bundle-branch block and left anterior hemiblock were induced in 17 cases. This association represented the second most frequent

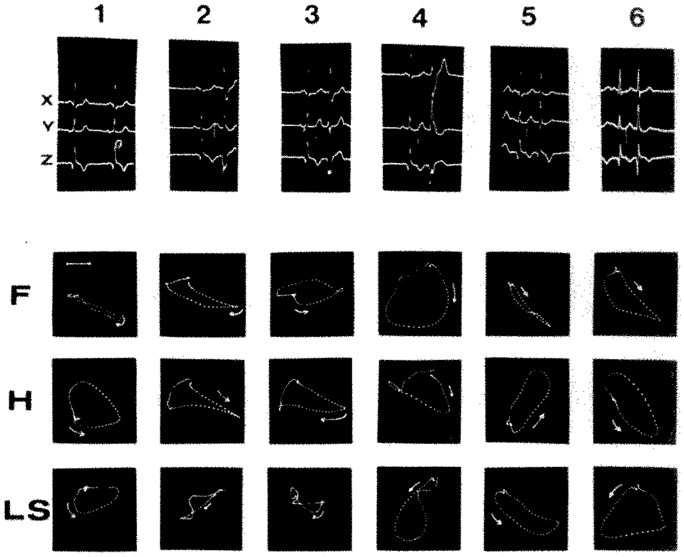

FIG. 3 *Tracings obtained from man aged 60 with peripheral vascular disease and normal resting electrocardiogram. 1: control tracing; 2: isolated right bundle-branch block; 3: left anterior hemiblock with right bundle-branch block; 4: left posterior hemiblock with right bundle-branch block; 5: slight modifications of QRS well displayed in horizontal plane, with leftward shift of the initial forces and attraction of both efferent and afferent limbs towards left posterior quadrant (slight degree of incomplete left bundle-branch block ?); 6: anterior displacement of initial and early forces of QRS with some signs suggesting tendency towards left posterior hemiblock. Loops are interrupted every 1·25 ms. Calibration: 0·5 mV.*

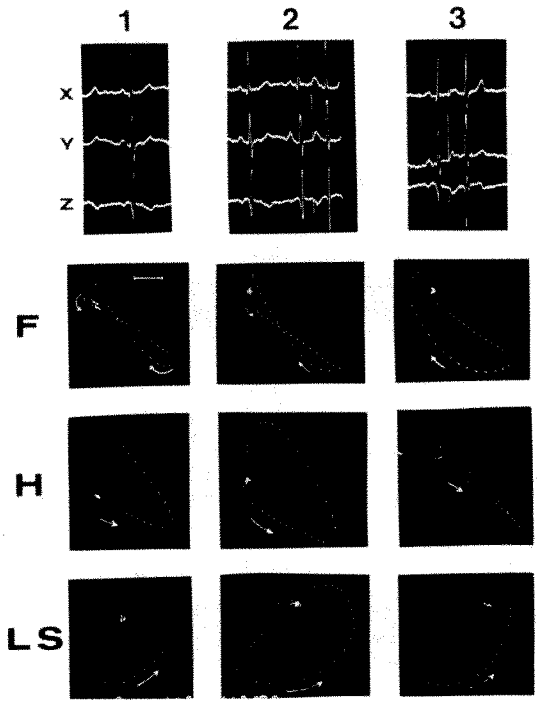

FIG. 4 *Tracings obtained from man aged 56, with history of previous myocardial infarction. Control tracing (1) is moderately abnormal and shows anterior displacement of horizontal maximal QRS vector with slightly prolonged anterior forces. Time required to reach maximum anterior voltage also exceeds normal values (>30 ms). These features are in keeping with old posterior lesion. In (2) and (3), aberrant conduction results in further increase of anterior forces. Concomitantly, initial vectors are displaced to left and frontal loop takes clockwise rotation instead of figure-of-eight which was present in control. Loops are interrupted every 1·25 ms. Calibration: 0·5 mV.*

pattern. The vectorcardiogram showed a type A morphology in 9 patients and a type B in 11. In 3 subjects, both morphologies were obtained during the same experiment. Finally, combined left posterior hemiblock and right bundle-branch block were induced in 11 patients (6 with the type A, and 5 with the type B).

Unclassified patterns

Twelve configurations of aberrant conduction could not be classified into the usual categories of intraventricular blocks. In 7, the alterations only consisted of a trivial modification of the QRS contour. In the remaining 5, the changes in QRS were much more conspicuous and rather unexpected. They consisted of a very significant anterior shift of the initial and early forces (Fig. 3). Three of these patients had a normal control vectorcardiogram; they developed aberrantly conducted beats in which the portion of the QRS area located anterior to the X axis exceeded 75 per cent and the duration of the anterior forces was much prolonged. The horizontal plane loop remained inscribed in a counterclockwise fashion. A similar, though less obvious anterior displacement of the initial forces took place in two further cases; one had a documented true posterior necrosis (Fig. 4), the other an anterior infarct. The electrical evidence of infarction was enhanced in the first instance and reduced in the second.

Conduction disturbance and myocardial infarction

In the group of 11 patients with documented myocardial infarction, 31 different aberrantly conducted complexes were recorded. On 3 occasions, the induced intraventricular conduction disturbance obscured the evidence of the pre-existing necrosis (2 instances of inferior wall infarction hidden by a left anterior hemiblock or left bundle-branch block; 1 instance of anteroseptal infarction hidden by a right bundle-branch block producing a clockwise and anteriorly displaced transverse plane loop). In all the other cases, by using previously proposed criteria (Kulbertus *et al.*, 1971; Benchimol and Desser, 1972; Chou *et al.*, 1974), the diagnosis of myocardial infarction could still be made, in spite of the intraventricular aberrant conduction.

It should be stressed that the posterior shift of initial forces seen in incomplete left bundle-branch block might lead to an erroneous diagnosis of anterior necrosis, whereas the anterior displacement described in the preceding paragraph could mimic a true posterior myocardial infarction.

Discussion

Recovery of excitability does not occur simultaneously in all the peripheral portions of the specialized intraventricular conduction system (Hoffman *et al.*, 1963, Van Dam, Hoffman, and Stuckey, 1964; Moe, Mendez, and Han, 1965). This feature accounts for the fact that, following atrial premature beats, impulse propagation may be altered because of a refractory state in parts of the usual conduction pathways. This results in aberrant ventricular conduction with morphological alterations of the QRS complex.

Recent studies have indicated that block frequently occurs at the level of the His bundle or bundle-branches, though it may also take place in the more distal portions of the intraventricular conducting system (Myerburg *et al.*, 1975a; Zipes *et al.*, 1975, Elizari, Greenspan, and Fisch, 1975). The degree of prematurity probably contributes to the determination of the site of block (Myerburg *et al.*, 1975b). One may reasonably expect that when the transmission delay involves only a limited number of peripheral Purkinje fibres, aberrant conduction will manifest itself by small variations of the QRS contour. Conversely, more extensive distal blocks as well as blocks in the proximal branches or subdivisions are likely to produce patterns of bundle-branch block, hemiblock, or bilateral conduction defect. In this study, as well as in others (Rosenbaum *et al.*, 1970), the commonest abnormality was right bundle-branch block, the next most frequently occurring anomaly being the association of right bundle-branch block with left anterior hemiblock. The reasons for this order of frequencies probably include differences in the length and in the duration of recovery time of each fascicle (Rosenbaum *et al.*, 1972).

Examples of aberrant conduction provide good material for studying the effects of any type of block on the human electrocardiogram or vectorcardiogram. Thus, some cases of aberrant conduction indicate that, even in its apparently chronic form, left anterior hemiblock may, after atrial premature stimulation, disappear or else be replaced by an isolated right bundle-branch block. The possible electrophysiological mechanisms that might explain such observations (supernormal phase of conduction; phase 4 block; discordance of conduction time and refractory periods) have been discussed by others (Rosenbaum *et al.*, 1972; Wu *et al.*, 1974).

As regards left posterior hemiblock, the present findings confirm that an abnormal rightward deviation of the maximal QRS frontal axis is not, as initially thought (Benchimol and Desser, 1971; Castellanos *et al.*, 1971), a prerequisite for the diagnosis of this type of partial left bundle-branch block. In fact, changes produced by left posterior hemiblock are often so small that the diagnosis can only be made by comparison with the control tracing (Strickland, Horan, and Flowers, 1972).

With right bundle-branch block, isolated or combined with partial left bundle-branch block, the present results corroborate, if still needed, the opinion that an anteriorly displaced, clockwise rotated horizontal plane loop is not, as stated in the past (Donoso *et al.*, 1955; Saltzman, Linn, and Pick, 1966), necessarily indicative of associated pathology, such as right ventricular hypertrophy or infarction of the posterior wall of the left ventricle, but may result from an abnormal pattern of cardiac excitation (Gardberg and Rosen, 1958; Scherlis and Lee, 1963; Penazola, Gamboa, and Sime, 1961; Cohen *et al.*, 1968; Kulbertus *et al.*, 1970a). It should be noted that, whereas in spontaneous right bundle-branch block, counterclockwise horizontal loops are more usually seen especially in individuals without obvious heart disease (Chou *et al.*, 1974; Witham, 1975), clockwise and anterior loops were found to be more frequent after atrial premature stimulation. The same observation was made by Cohen *et al.* (1968). No explanation has been suggested for this finding.

Finally, our data further illustrate that the presence of conduction disturbances, including hemiblocks (Rosenbaum *et al.*, 1970; Durrer, 1972), may modify in a dramatic fashion the electrocardiographic manifestations of myocardial infarcts and thus, sometimes, hamper their diagnosis. Concealment of an anteroseptal infarction by a type B right bundle-branch block deserves to be emphasized.

In addition to these mainly confirmatory data, the results reported in this paper point to a less well-known aspect of aberrant conduction. They indicate that the vectorcardiographic pattern characterized by an increase in amplitude and duration of the anterior forces can be the consequence of a conduction disturbance.

Prominent anterior forces are generally interpreted as being a result of right ventricular hypertrophy or posterior myocardial infarction. Many criteria, often deceptive, have been proposed to discriminate between those two conditions (Mathur and Levine, 1970; Kini and Pipberger, 1974), the differential diagnosis becoming important particularly in older patients who may have coronary artery disease, or pulmonary emphysema, or both.

In a study of 360 patients whose vectorcardiogram showed prolonged anterior forces, Mathur and Levine (1970) found 203 clear-cut instances of right ventricular hypertrophy and 85 of posterior wall myocardial infarction. There remained, however, 72 cases which failed to show any evidence for either diagnosis. Witham (1975) states, with some reservations, that such unusual anterior displacement of the QRS might represent a normal variant in the older age-group. Our results show that it may be related to a conduction disturbance. At the present stage of our knowledge, it seems impossible to specify where the conduction delay responsible for this vectorcardiographic abnormality actually takes place.

It has frequently been assumed that right bundle-branch block does not alter the first half of QRS. Boineau, Spach, and Ayers (1967) have, however, clearly showed that this opinion was erroneous.

At present, the fact that right bundle-branch block, alone or combined with a left divisional block, is not uncommonly associated with an anterior shift of the horizontal plane loop, is a well-known phenomenon. No proof has been provided to show that this anterior displacement is exclusively the result of the right-sided disturbance. None the less, there is a possibility that some kind of right bundle-branch conduction defect does account for the vectorcardiographic abnormality seen in the 5 cases under discussion.

On the other hand, one should also remember that the anatomy of the left bundle-branch seems more complicated than expected from the currently widely accepted bifascicular representation. Indeed, in addition to the anterior and posterior subdivisions, there is a considerable contingent of centroseptal fibres (Demoulin and Kulbertus, 1972), and all the peripheral subdivisions are interconnected by a very rich plexus of anastomoses. The interior network is thus very extensive (Lazzara, Yeh, and Samet, 1974; Myerburg *et al.*, 1975b), and it seems reasonable to suggest that, at times, anterior or posterior segments within this distal Purkinje network might be the site of delayed activation; this could also possibly result in shifts of the horizontal axis of QRS.

Further studies are surely needed to determine, on a firm basis, which part of the atrioventricular transmission system is involved in the conduction delay responsible for the prominent anterior forces observed in some of our cases.

The purpose of this discussion was merely to emphasize that, in addition to right ventricular hypertrophy and posterior infarction, conduction disturbances should be considered as a possible aetiology in the clinical interpretation of such tracings.

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Morphogenesis of univentricular hearts

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Two main theories exist for the explanation of univentricular hearts. One states that the bulboventricular septum becomes realigned to form the interventricular septum, and that univentricular hearts are a consequence of failure of this realignment. The other states that bulboventricular and interventricular septa are different structures, and that the univentricular heart results from failure of formation of the posterior interventricular septum. Four hearts are described in which both the posterior septum and an anterior bulboventricular septum are present. In each heart, therefore, the right ventricular sinus is separated both from the left ventricular sinus and from a discrete outlet chamber which supports the pulmonary artery. It is argued that these findings militate strongly against theories proposing reorientation of the bulboventricular septum to form the definitive interventricular septum. They support strongly the concept that the definitive right ventricle is formed in part from the bulbus and in part from the primitive ventricle. On the basis of these findings, it is suggested that the distinctive feature of the univentricular heart is absence of the posterior septum. Such hearts can properly be termed 'primitive ventricle'. It is also suggested that hearts with atretic or straddling valves should be included within this category.

For some considerable time, hearts with one effective ventricular chamber have been the topic of controversy and confusion. In recent years much of this disagreement has centred upon differences in opinion regarding the correct usage of the terms 'single' and 'common' ventricle, as applied to these hearts (Lev, Paul, and Miller, 1962; Van Praagh, Ongley, and Swan, 1964; Somerville, Becu, and Ross, 1974). Other points of contention are more fundamental and relate to differing theories regarding the embryogenesis of both the normal right ventricle and the univentricular heart. Keith (1906, 1909) pointed out that the primitive bulbus formed only part of the definitive right ventricle, and that the bulbus could persist as a discrete cardiac chamber. The concept that the primitive ventricle formed the sinuses of both right and left ventricles subsequently received support from the embryological investigations of Pernkopf and Wirtinger (1933). Both Harley (1958) and Lev *et al.* (1969) subsequently suggested that the main chamber in univentricular hearts was composed of both right and left ventricular sinuses. In contrast, the studies of Streeter (1942, 1945, 1948) had indicated that the trabeculated pouch of the right ventricle was a derivative of the primitive bulbus. From this finding, others assumed that the primitive bulbus formed the entirety of the definitive right ventricle, and that the embryonic primitive ventricle formed only the definitive left ventricle (de Vries and Saunders, 1962). Since the primitive ventricle originally received blood from both right and left atria, de la Cruz and Miller (1968), therefore, argued that 'single ventricle with outlet chamber' resulted from failure of migration of the right atrioventricular canal from the primitive ventricle to the bulbus. Since they believed the primitive ventricle formed only the left ventricle, they suggested that these hearts should be termed 'double inlet left ventricle'. Van Praagh *et al.* (1964) had previously argued in similar fashion, but had concluded that the right ventricular sinus was absent in 'single ventricle with outlet chamber'. The keystone of this controversy is, therefore, the fate of the original septum between the primitive bulbus and the primitive ventricle (Fig. 1). If this septum is considered as possessing right and left parts, which can be termed ridges, applying the

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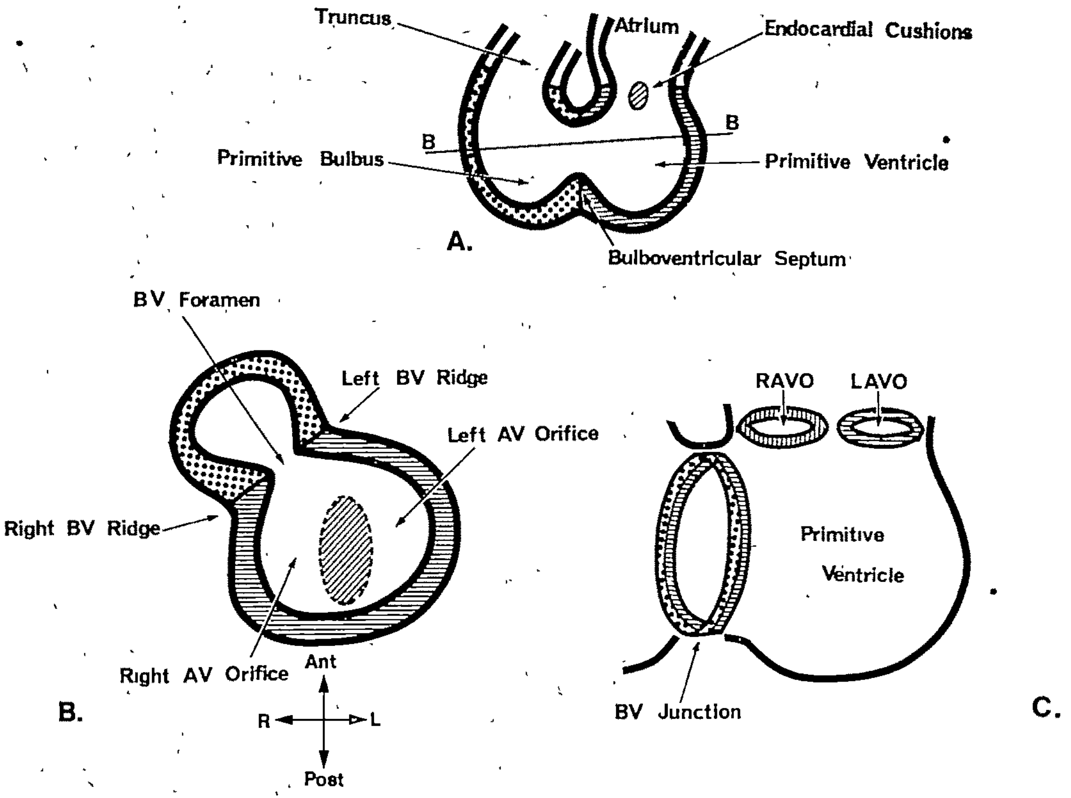
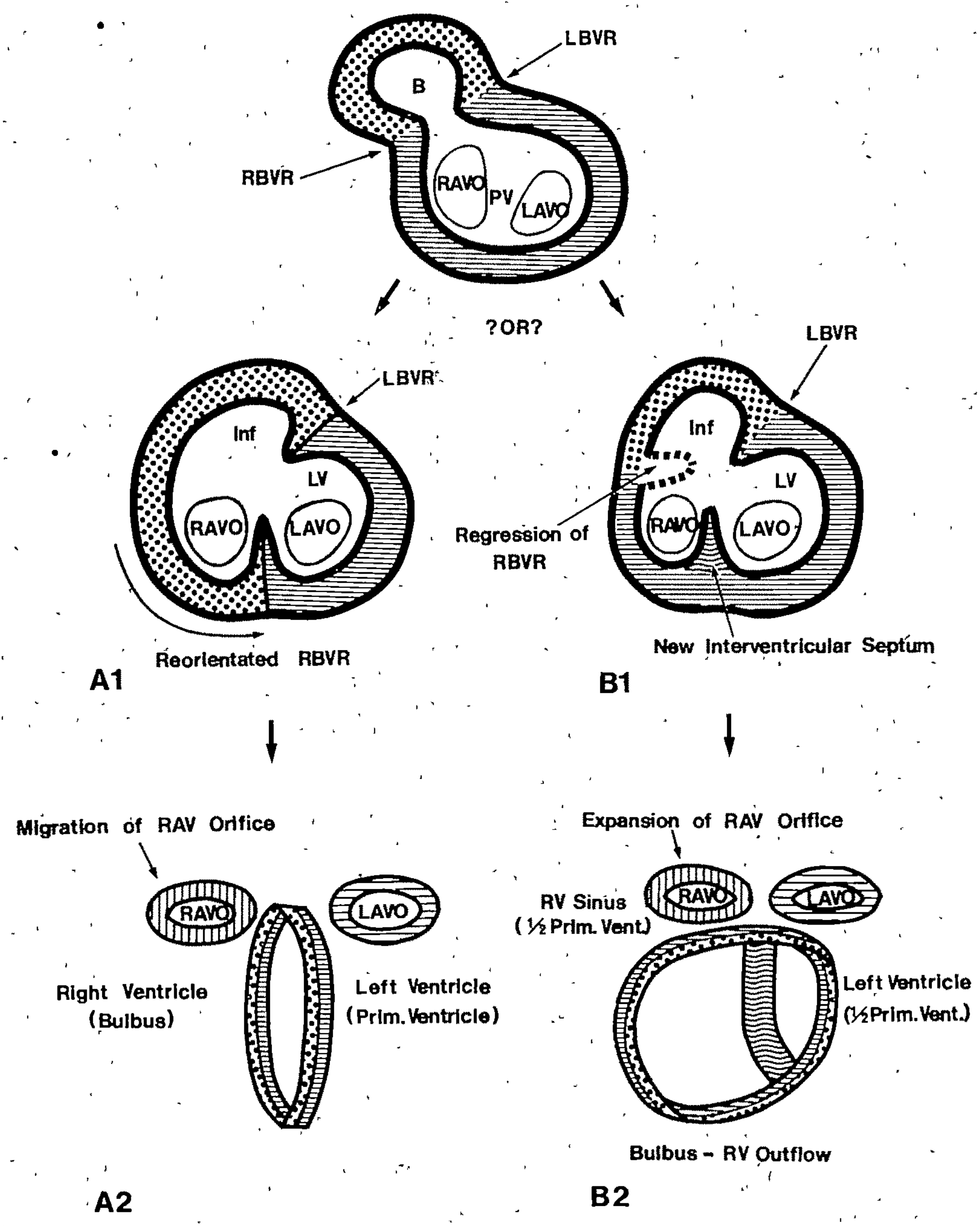


FIG. 1 *Diagrammatic representations to illustrate the form of the primitive heart tube following bulboventricular looping. (A) View of a frontal section through the loop. The primitive atrium communicates only with the primitive ventricle. The junction between the two, the atrioventricular canal, is becoming septated by the endocardial cushions to form the right and left atrioventricular orifices (RAVO, LAVO) which perforce will open into the primitive ventricle. The primitive ventricle opens to the primitive bulbus through the bulboventricular foramen. This foramen is bounded inferiorly by the bulboventricular septum, superiorly by the inner curvature of the heart tube (conoventricular flange), and to right and left by the bulboventricular (BV) ridges. The bulbus supports the truncus, which leads to the aortic sac. (B) Section through the loop at level B-B. (C) Relation at this stage between the bulboventricular foramen and the atrioventricular orifices. The cross-hatching will remain constant throughout the succeeding figures.*

theory of Streeter (1942) to development it can be seen that active migration of the right atrioventricular canal would convert the right bulboventricular ridge into the posterior interventricular septum (Fig. 2A). In contrast, application of the concept of Pernkopf and Wirtinger (1933) reveals that regression of this ridge would be required during development, with subsequent growth of a new posterior septum to divide the primitive ventricle (Fig. 2B).

If it could be shown that a heart existed in which a posterior septum divided the right and left ventricular sinuses, while in the same heart an anterior septum divided the ventricular inflow portions from an outlet chamber, this finding would constitute strong evidence in favour of the concept for development of 'single ventricle with outlet chamber' espoused by Harley (1958) and Lev *et al.* (1969). It would militate against the arguments of Van Praagh *et al.* (1964) and de la Cruz and Miller (1968) (Fig. 3). We have recently examined four such hearts. The findings are described here and it is suggested that they form the basis for a classification of the univentricular heart.


LBVR
B
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PV
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Reorientated RBVR
A1
LBVR
Inf
LV
Regression of RBVR
RAVO
LAVO
New Interventricular Septum
B1
Migration of RAV Orifice
RAVO
LAVO
Right Ventricle (Bulbus)
Left Ventricle (Prim. Ventricle)
A2
Expansion of RAV Orifice
RV Sinus (½ Prim. Vent.)
RAVO
LAVO
Left Ventricle (½ Prim. Vent.)
Bulbus - RV Outflow
B2

FIG. 2. *Diagrams illustrating the different theories regarding the mode of development of the definitive right ventricle. The primitive state is shown in the upper figure (B—bulbus; PV—primitive ventricle; LBVR, RBVR—left and right bulboventricular ridges; RAVO, LAVO—right and left atrioventricular orifices). Series A illustrates the theory espoused by de la Cruz and Miller (1968). They suggested that the right bulboventricular ridge becomes reorientated after migration of the right AV orifice. The RBVR becomes the posterior interventricular septum. The definitive right ventricle is consequently formed entirely from the bulbus, while the primitive ventricle forms only the definitive left ventricle. The relations of the AV orifices to the BV foramen following this process are illustrated in Fig. 2A2. In contrast, Lev* et al. *(1969) suggested that the primitive ventricle contributed to both ventricular sinuses. This mechanism is illustrated in Fig. 2B. Expansion of the atrioventricular canal and regression of the right BV ridge enables both bulbus and primitive ventricle to contribute to the definitive right ventricle. A new septum is formed in the primitive ventricle dividing the chamber into the definitive right and left ventricular sinuses. The anticipated relations of the AV orifices to the BV foramen after this mode of development are illustrated in Fig. 2B2. When applied to the anomaly of the univentricular heart, Theory A would result in this anomaly following failure of migration of the right AV orifice from the primitive ventricle to the bulbus. If this theory were correct, the univentricular heart would indeed be a 'double inlet* left *ventricle'. However, Theory B would account for this anomaly as a consequence of failure of septation of the primitive ventricle and persistence of the right bulboventricular ridge. If this theory were correct, it would be inappropriate to label this anomaly 'double inlet left ventricle'; 'double inlet* primitive *ventricle' would be the correct term.*

Description of specimens

Case 1

This heart was from the cardiopathological collection of Grimsby General Hospital. Only the heart was available for examination. The arch and apex were both to the left in the presence of atrial situs solitus. The pulmonary artery was anterior and to the left of the aorta, the great arteries being of similar size. The coronary arteries were normally arranged with right dominance, but a large right marginal artery was seen (Fig. 4A). The right atrium received the superior and inferior caval veins and the coronary sinus. There was a large ostium primum defect between right and left atria, with an additional small patent foramen ovale. The left atrium received the four pulmonary veins. At first sight it appeared that a common atrioventricular valve was present. However, on closer examination (Fig. 4B) it was seen that the lower edge of the atrial septum straddled the left ventricle which received a normal mitral valve. The interventricular septum was deviated to the right as a consequence of gross hypoplasia of the right ventricular inflow portion. On opening this small chamber (Fig. 4C) it was found to contain a separate but hypoplastic tricuspid valve. The aorta arose from the large left ventricle and fibrous continuity was present between the aortic and mitral valves. The pulmonary artery arose from a discrete anterior outlet chamber. This chamber (Fig. 4D) possessed a smooth upper portion and a trabeculated apical portion. It communicated with the hypoplastic right ventricular inflow segment through a slit-like apical defect, and also with the left ventricle through a small subaortic defect. The diagnosis was: (1) Solitus concordant-normal connexions; (2) ostium primum atrial septal defect; (3) hypoplasia of right ventricular sinus and tricuspid valve; (4) origin of pulmonary artery from discrete outlet chamber.

Cases 2 and 3

Case 2 was also from the cardiopathological collection of Grimsby General Hospital. Case 3 was from the collection of the Royal Liverpool Children's Hospital. The hearts were similar in appearance and can be best described by reference to Case 3. The heart alone was available for examination. The atria were in solitus position and the arch and apex were to the left. The pulmonary artery was anterior and to the left of the aorta, and was slightly smaller than the aorta (Fig. 5A). The coronary artery distribution was normal, with right dominance. The right atrium received the superior and inferior venae cavae and the coronary sinus. The atrial septum was closed. The left atrium received the four pulmonary veins. Both atria communicated through separate atrioventricular valves with a partially septated ventricular cavity (Fig. 6A). The left atrioventricular valve was tethered by two pairs of multiple papillary muscles joined together at the ventricular apex (Fig. 5C). This part of the

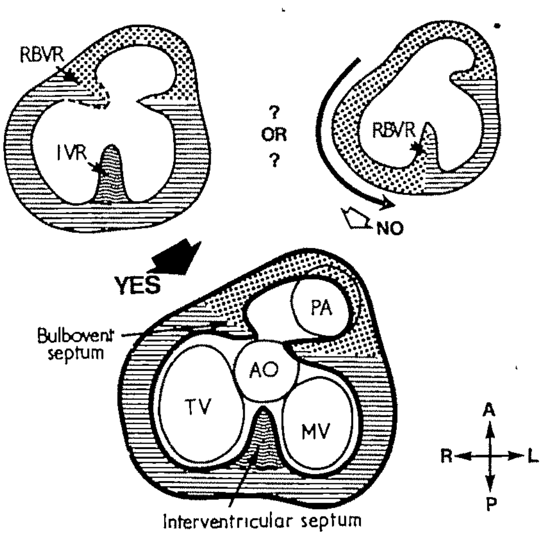


FIG. 3 *This diagram illustrates the relations between the two theories of development described in Fig. 2 (upper panels) and a theoretical heart. If Theory B were correct, it would be anticipated that a heart would exist in which the bulvoventricular septum persisted to separate the right ventricular outflow tract (bulbus) from the sinus (primitive ventricle). At the same time, the right ventricular sinus could be separated from the left ventricular sinus, both derived from the primitive ventricle, by the posterior interventricular septum, itself derived from the primitive ventricle. Such a heart is shown in diagrammatic form in the lower panel (TV—tricuspid valve; MV—mitral valve; AO—aorta; PA—pulmonary artery; IVR—interventricular ridge; other abbreviations as before). The diagram illustrates that it is difficult to account for this heart by application of the theory which assumes reorientation of the right BV ridge to form the posterior interventricular septum.* →

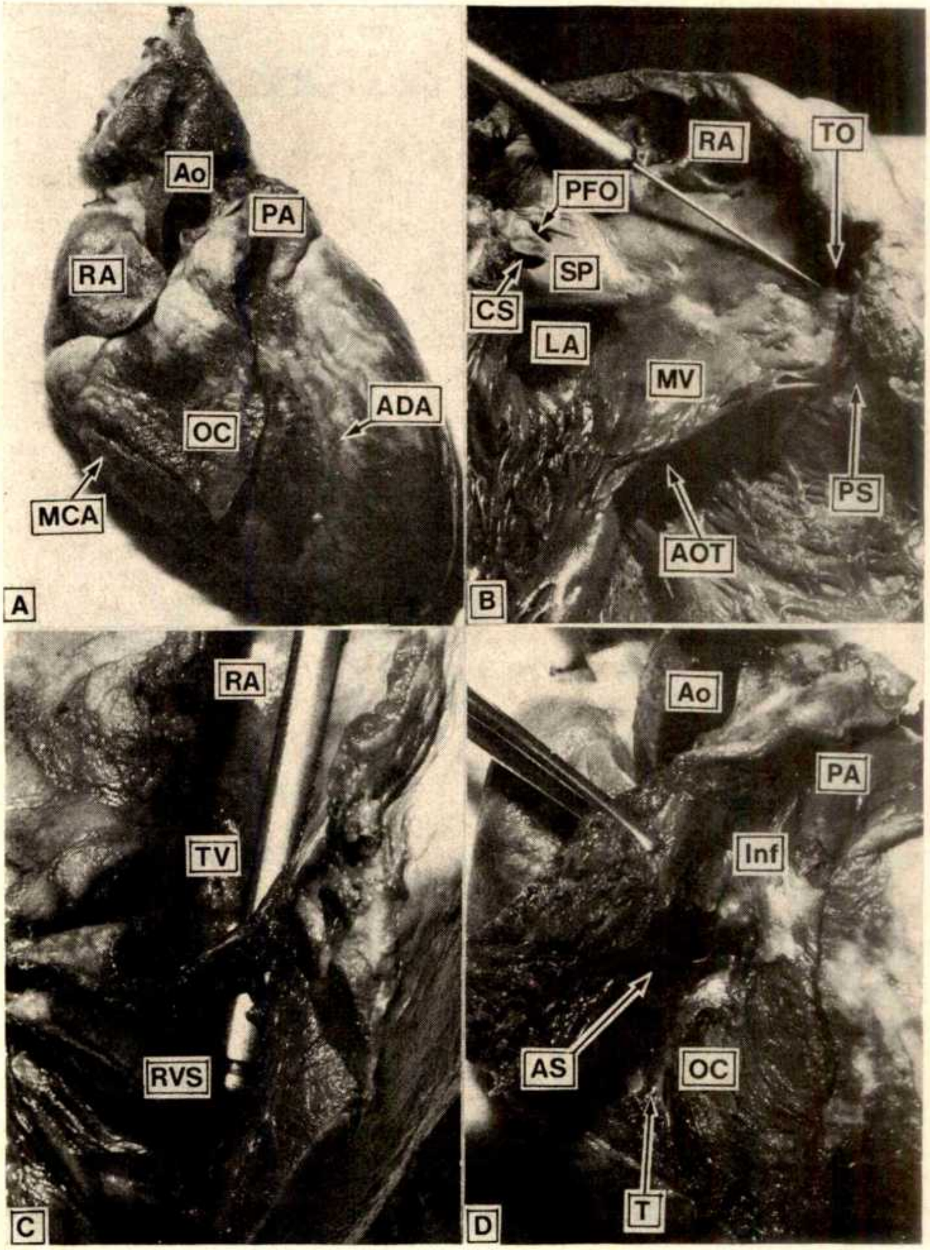
main ventricular cavity was coarsely trabeculated (Fig. 5C, D). The right atrioventricular valve was tethered posteriorly by multiple small papillary muscles and anteriorly was tied down by short chordae to an anterior septum. A larger anterior papillary muscle arose from the posterior aspect of this septum (Fig. 6B). Posteriorly the ventricular cavity was partially divided by a ridge-like septum which swept down to form a shallow apical septum (Fig. 6A). Anteriorly it swept up to fuse with the anterior septum (Fig. 6B). This posterior septum was coarsely trabeculated on both sides (Fig. 5C, 6B) and was overriden by the aortic valve which was in continuity with both the right and left atrioventricular valves (Fig. 5D, 6A). A further defect was present beneath the tied-down anterior cusp of the right atrioventricular valve (Fig. 5D, 6C). This defect passed into a discrete anterior outlet chamber which gave rise to the pulmonary artery. This outlet chamber had a trabeculated apical segment and a smooth upper segment (Fig. 5B). The posterior wall of the smooth segment was in part derived from the conus septum between aorta and pulmonary artery. Some of the chordae tethering the anterior cusp of the right atrioventricular valve were arising from the outlet chamber aspect of the anterior septum (Fig. 5B). The diagnosis in both cases was: (1) solitus-primitive ventricle-normal connexion; (2) partial septation of primitive ventricle; (3) pulmonary artery from discrete outlet chamber.

Case 4

This heart was present in the anatomical museum

FIG. 4 *Photographs of Case 1. (A) Anterior view of the heart. The aorta and pulmonary artery (AO, PA) are normally connected and related. The outlet chamber (OC) is delimited by the anterior descending coronary artery (ADA). (RA—right atrium; MCA—marginal branch of right coronary artery.) (B) Atrioventricular junction opened from behind through a cut in the left ventricle. The deviated posterior septum is seen (PS) with the mitral valve (MV) attached to its crest. The aortic outflow tract (AOT) is seen beneath the anterior cusp of this valve. The pointer indicates the hypoplastic right ventricular sinus which receives the tricuspid orifice (TO). An ostium primum defect is present and the lower edge of the septum primum (SP) straddles the left ventricle. The left atrium (LA) is seen beneath this through the primum defect. (CS—coronary sinus; PFO—patient foramen ovale.) (C) Hypoplastic right ventricular sinus (RVS) opened from behind. The hypoplastic tricuspid valve (TV) is tethered into this cavity. (D) The outlet chamber which supports the pulmonary artery has smooth infundibular (Inf) and apical trabeculated (T) portions. It is separated from the ventricular inflow portions by a well-formed anterior septum (AS).* →

of St. Bartholomew's Hospital Medical School, London, and was brought to our attention by Professor O. J. Lewis. The atria were arranged in situs solitus and the arch and apex were to the left. The pulmonary artery was anterior and to the left of the aorta, and was about two-thirds of the size of the aorta. There was dominance of the right coronary artery, and a prominent right marginal branch was observed (Fig. 7A). The venous drainage was normal, and the atrial septum was closed. The right atrium drained to a coarsely trabeculated ventricular sinus which was septated both from the left ventricle and from the right ventricular outflow portion (Fig. 7B-D). The valve in the right ventricular sinus was typical of a tricuspid valve, having multiple posterior papillary muscles, a large anterior



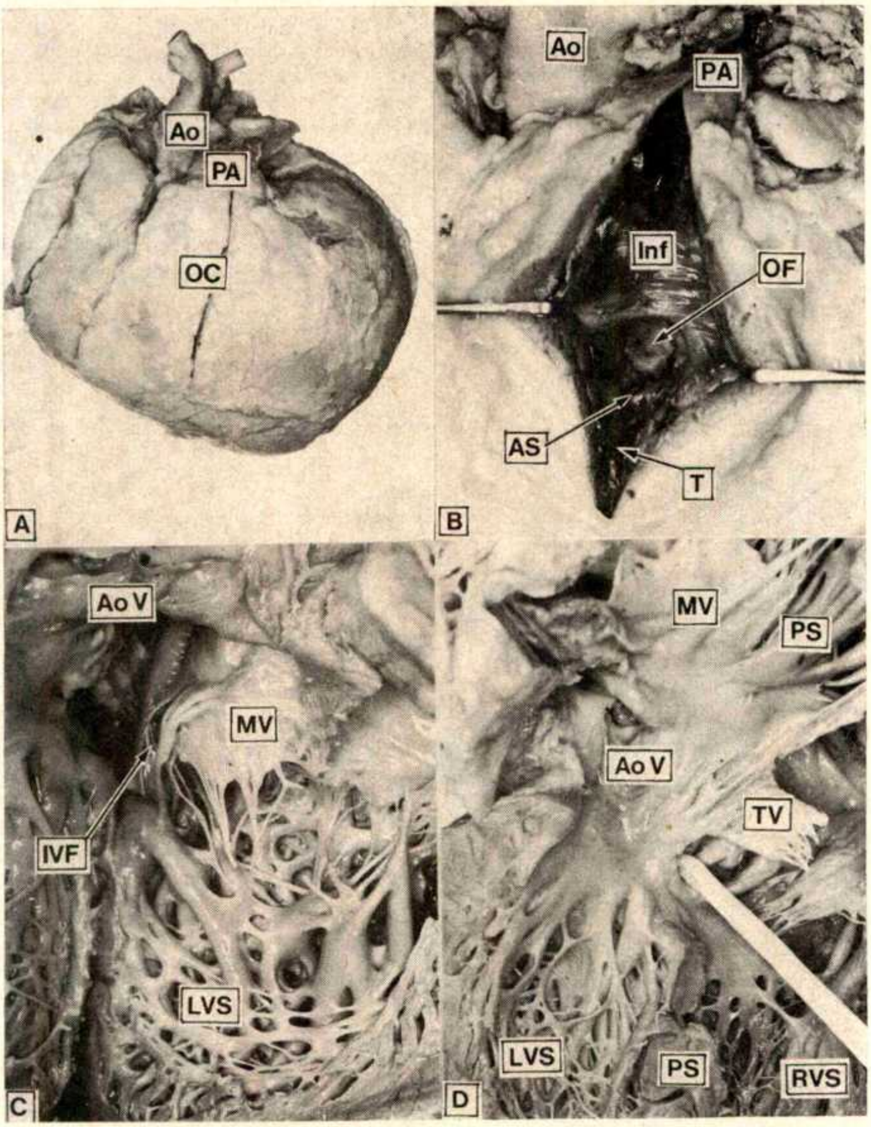


FIG. 5 *Photographs of Case 3. (A) Anterior view of the heart. The great arteries (Ao, PA) are normally connected and related. The pulmonary artery arises from an anterior outlet chamber (OC). (B) Opened outlet chamber, which has a smooth upper infundibular portion (Inf) and an apical trabeculated segment (T). Note that the tricuspid valve is visible above the anterior septum (AS) through the outlet foramen (OF). (C) Left ventricular inflow tract. The mitral valve (MV) enters a coarsely trabeculated sinus (LVS) and communicates with the right ventricular sinus through an interventricular foramen (IVF). The aorta (AoV—aortic valve) overrides this foramen. (D) Anterior aspect of both ventricular inflow tracts, opened through a sagittal cut in the main ventricular chamber. The posterior part of the chambers is reflected to the top right part of the figure, and a posterior septum (PS) is seen separating the mitral and tricuspid valves (MV, TV), both being in continuity with the aortic valve (AoV). The anterior wall of the chamber is separated into right and left sides (RVS, LVS) by the shallow posterior septum (PS). The probe is placed in the outlet foramen beneath the tricuspid valve.*

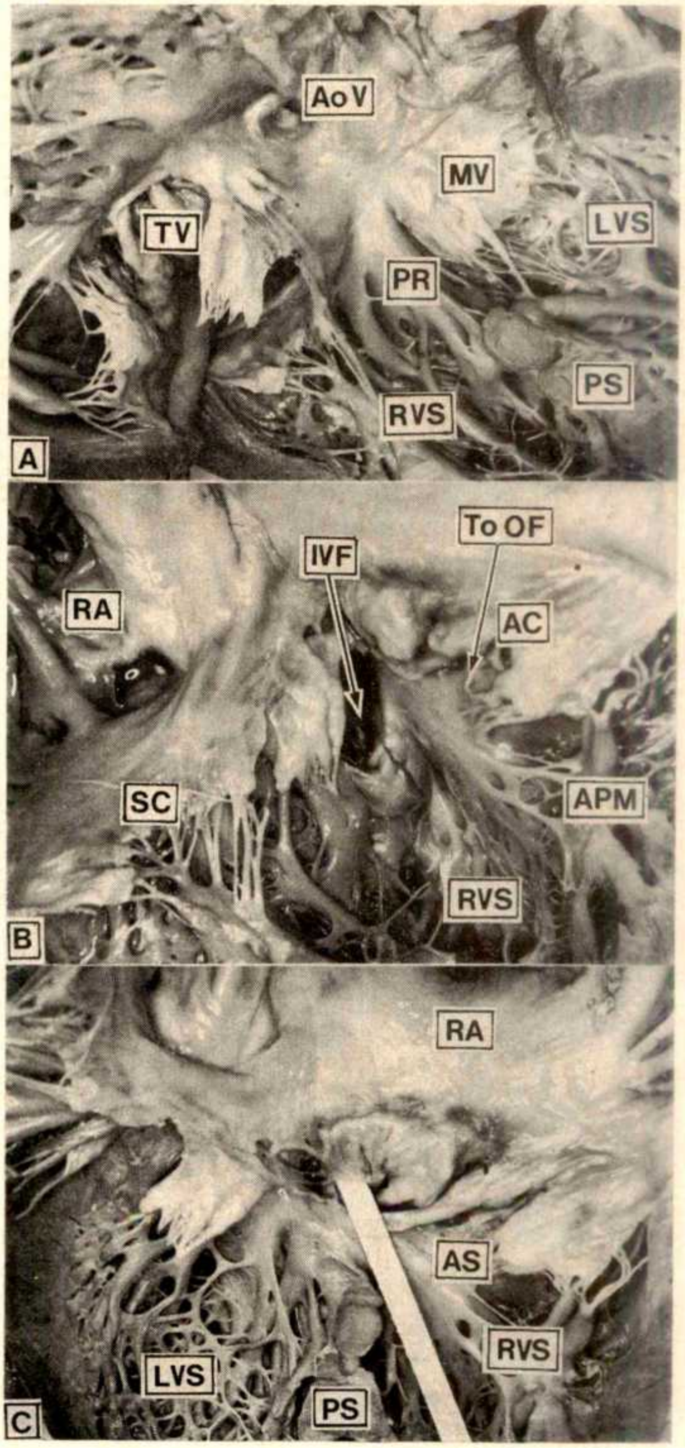


FIG. 6 *Further photographs of Case 3. (A) Posterior wall of the main ventricular chamber, opened as described for Fig. 5D. The atrioventricular valves (TV, MV) are both in continuity with the aortic valve (AoV). The right and left ventricular sinuses (RVS, LVS) are separated by the posterior septum (PS), which approximates posteriorly to the ridge (PR) seen in primitive ventricular hearts. (B) View of the right ventricular sinus opened through its parietal wall. The right atrium (RA) communicates with this sinus (RVS) through the tricuspid valve. The septal (SC) and anterior (AC) cusps are seen, and the interventricular foramen (IVF) is visible. The outlet foramen is beneath the anterior cusp (To OF). (APM—anterior papillary muscle.) (C) Further view of the anterior parts of the ventricular inflow tracts opened through the sagittal incision described above. The probe is placed through the outflow foramen. Note that the anterior septum (AS) is separate from the posterior septum (PS).*

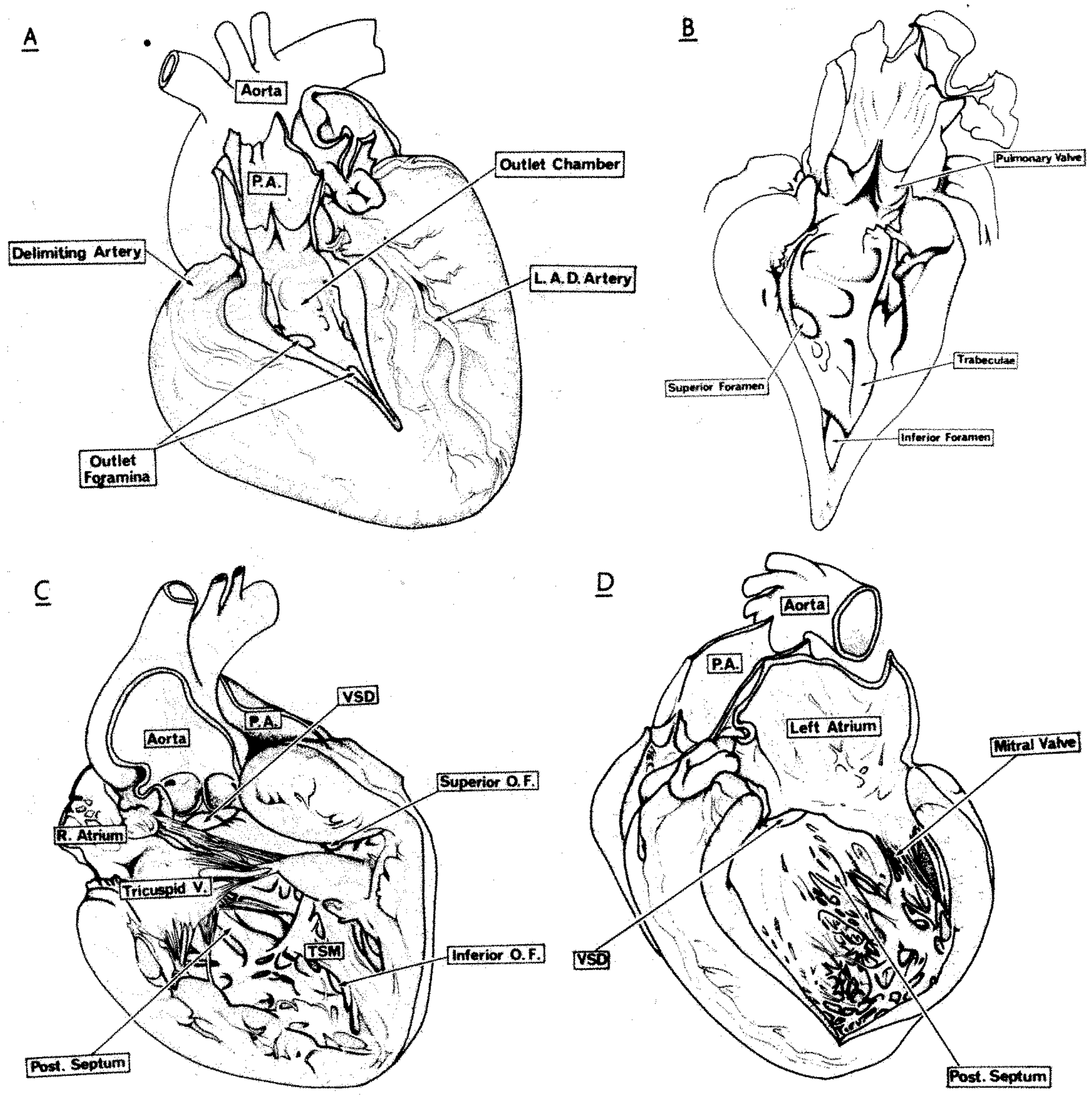


FIG. 7 *Drawings of Case 4. The heart was in a 'pot' in the anatomical museum of St. Bartholomew's Medical School, and could not be adequately photographed. (A) Anterior aspect of the heart, with the pulmonary artery (PA) arising from a discrete outlet chamber which is delimited by the anterior descending (LAD) and marginal coronary arteries ('delimiting artery'). (B) Detail of the outlet chamber with two outlet foramina. (C) Right ventricular inflow portion (VSD—ventricular septal defect; TSM—trabecula septomarginalis; OF—outlet foramen). (D) The left side of the heart.*

papillary muscle, and a conal papillary muscle (Fig. 7C). The posterior septum was well formed and trabeculated on its right aspect. The left aspect was smooth, and a typical morphologically left ventricular sinus received a valve with morphological characteristics of the mitral valve (Fig. 7D). The aorta overrode a large defect between the right and left ventricular sinuses, and there was fibrous continuity between the aortic and mitral valves. The septum separating the right ventricular sinus from the outlet chamber was overlaid on its posterior aspect by a large trabecula septomarginalis which gave rise to conal and anterior papillary muscles (Fig. 7C). Defects were present between right ventricular sinus and outlet chamber both above and beneath the trabecula (Fig. 7C). The outlet chamber was a well-formed structure and possessed a smooth upper portion and a large apical segment which received both defects from the right ventricular inflow tract (Fig. 7B). The prominent marginal artery marked the position of the right part of the septum between inflow and outflow chambers (Fig. 7A).

The diagnosis was: (1) Solitus-concordant-normal connexions; (2) Fallot's tetralogy; (3) origin of pulmonary artery from discrete outlet chamber.

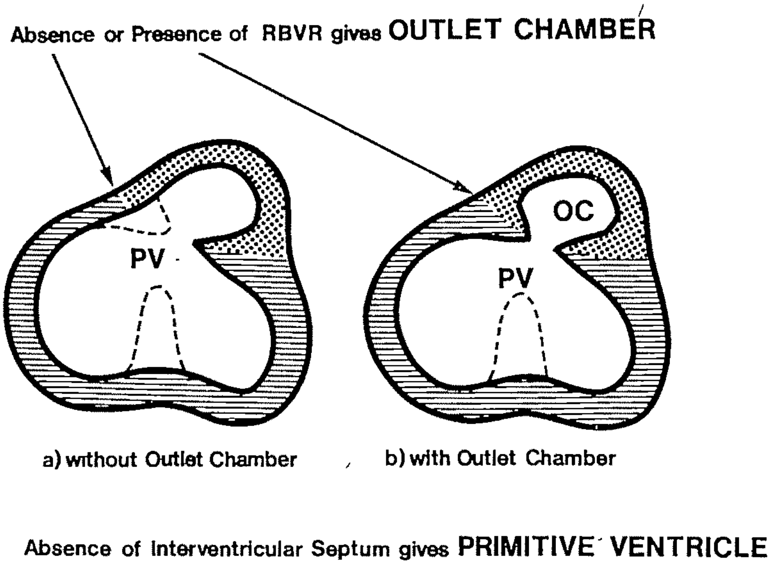
Discussion

The hearts described here have in common the feature that in each heart the anterior great artery (pulmonary artery) arose from a discrete outlet chamber. It is significant that this outlet chamber observed is directly comparable to the outlet chamber seen in 'single ventricle with outlet chamber' when this outlet chamber *also supports the pulmonary artery*. This situation in 'single ventricle' is frequently referred to as the 'Holmes' heart (Holmes, 1824; Rosenquist, Olney, and Roe, 1963; Marin-Garcia *et al.*, 1974; Somerville *et al.*, 1975). It is further significant that such outlet chambers are also directly comparable with the so-called 'right ventricle' seen in tricuspid atresia with normally connected great arteries (Edwards *et al.*, 1965; Gasul, Arcilla, and Lev, 1966).

The hearts described also have in common the fact that though the outlet chamber is separated from the right ventricular sinus by a well-formed anterior septum, the right ventricular septum is separated from the left ventricular sinus by a posterior septum of varying dimensions and proportions. In two of the hearts (Cases 2 and 3), this posterior septum is comparable with the 'posterior ridge' seen in 'single ventricle with outlet chamber' (Lev *et al.*, 1969; Anderson *et al.*, 1974). In one heart (Case 1), the septum is well formed but is deviated as a consequence of hypoplasia of the right ventricular sinus. In the remaining heart (Case 4) the posterior septum is directly comparable to the normal interventricular septum, and indeed the relations between this septum and the aorta are as seen in Fallot's tetralogy. In each case, therefore, it is as though the right ventricle were divided into two portions, and 'two-chambered right ventricle' would be an alternative designation for each of the hearts. In this respect, Case 4 is very similar to some of the hearts recently reported within this designation by Rowland, Rosenthal, and Castaneda (1975).

The important feature of these hearts is that in each case discrete and different septa divide the inlet portions of the heart from each other and from an outlet chamber. This is of major significance in relation to hearts in which an outlet chamber is separated from a main ventricular chamber by an anterior septum, but in which the main chamber is unseptated and receives both atrioventricular valves ('single ventricle with outlet chamber'). De la Cruz and Miller (1968) have argued that in these hearts the anterior septum is the malaligned posterior septum. It is supposedly in anterior position as a consequence of failure of migration of the right atrioventricular canal to the bulbus. They quote as further evidence in support of this concept the fact that hearts are found in which the right valve straddles the anterior septum, arguing that these hearts are intermediate specimens in the process of migration of right atrioventricular orifice from left ventricle to bulbus. It is clear that the hearts presently described constitute important evidence against this hypothesis. Since both anterior and posterior septa are present in the same specimens, the one could not possibly be formed by realignment of the other as is implied by the concept of de la Cruz and Miller (1968).

It can be argued from our data that the anterior septum between the outlet chamber and right ventricular sinus is the original bulboventricular septum, while the posterior septum is the septum derived from growth within the primitive ventricle. This presumes that the right ventricle is developed after regression of the original right bulboventricular septum. However, it could equally be argued that the anterior septum is a 'false' septum, derived from the extensions of the conus septum together with the trabecula septomarginalis, as suggested by Lev (Gasul *et al.*, 1966; Lev *et al.*, 1969). Alternatively the 'septum' could be derived from anomalous insertion of the trabecula septomarginalis (or moderator band) as suggested by Rowland *et al.* (1975). Whatever the origin of the septum, there is no doubt in our minds that the septa seen in the hearts described here are directly


Absence or Presence of RBVR gives OUTLET CHAMBER
PV
OC
PV
Absence of Interventricular Septum gives PRIMITIVE VENTRICLE

a) without Outlet Chamber
b) with Outlet Chamber

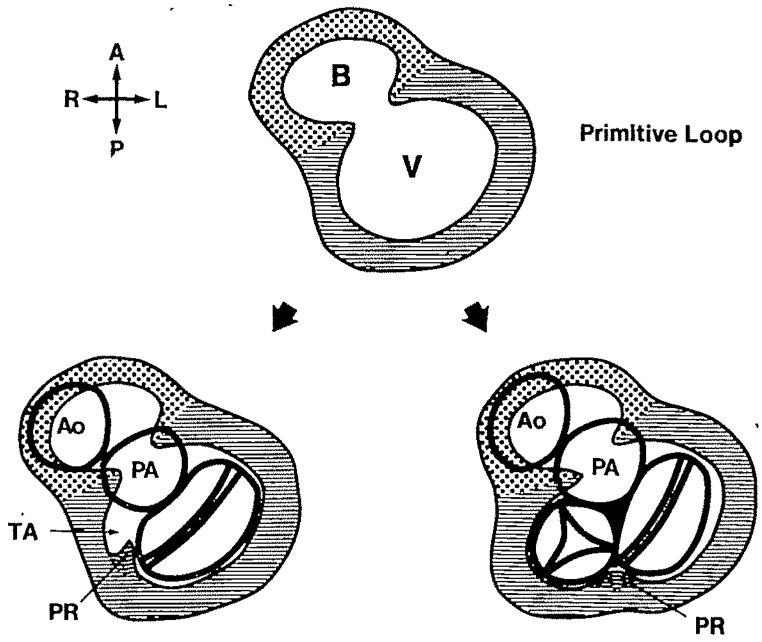
FIG. 8 *Diagrams illustrating the concept of classification of univentricular hearts as 'primitive ventricle'. Primitive ventricle can be defined as absence of the posterior interventricular septum. Presence or absence of the right bulboventricular ridge (RBVR) then enables primitive ventricles to be classified as either 'primitive ventricle with outlet chamber' or 'primitive ventricle without outlet chamber'.*

comparable with the septa seen in 'single ventricle with outlet chamber'. We suggest that if this septum is 'false' in one category, it is also false' in the other. Further evidence is pertinent to this problem. Van Praagh *et al.* (1964) had suggested that conducting tissue studies would solve the problem concerning the nature of the septum. Our own studies indicated that the septum in 'single ventricle with outlet chamber' carried both the atrioventricular bundle and bundle-branches (Anderson *et al.*, 1974). This finding was confirmed by Bharati and Lev (1975). However, these histological results still did not indicate whether the septum was in its anterior position as a consequence of failure of migration of the right atrioventricular orifice or persistence of the right bulboventricular ridge. We now believe that the present findings indicate that the anterior septum is indeed a persistent right bulboventricular ridge, and our gross studies in Cases 2 and 3 suggest that the anterior septum carries conducting tissue. We await histological confirmation of this fact. We, therefore, submit that the evidence presented indicates that, as suggested by Keith (1906) and endorsed by Lev *et al.* (1969), the definitive right ventricular sinus is a derivative of the primitive ventricle while the outlet portion can persist as a discrete chamber derived from the primitive bulbus.

Although the premise of de la Cruz and Miller (1968) assumes that the primitive ventricle contributes only to the definitive left ventricle, these workers agree that the embryonic primitive ventricle initially receives the atrioventricular canal in its entirety. Lev *et al.* (1969) pointed out that whichever theory of development was adopted, it would always be correct to speak of the chamber receiving the atrioventricular valves in univentricular hearts as the *primitive ventricle*. We suggest that this can be extended to provide the basis of an alternative classification for the univentricular heart which totally avoids the use of the contentious terms 'single', 'common' or 'double inlet left' ventricle

Primitive ventricle can properly be defined in anomalous conditions as absence of the posterior interventricular septum (Fig. 8). It can then be subdivided, depending upon presence or absence of the anterior bulboventricular septum, into *primitive ventricle with outlet chamber and primitive ventricle without outlet chamber* (Fig. 8).

This concept can be taken further. We indicated above that the outlet chambers in the hearts we have described are directly comparable with the so-called right ventricle seen in tricuspid atresia. At present it is usual to exclude hearts with atresia of an atrioventricular orifice from the category of the univentricular heart (Van Praagh *et al.*, 1964; Gasul *et al.*, 1966). No scientific reason is given for this exclusion. We believe that the similarity in chamber morphology makes the exclusion unwarranted. Furthermore, we contend that the similarities are related to the fact that tricuspid atresia is morphogenetically linked to primitive ventricle. It has previously been argued by others that primitive ventricle itself results from lack of migration of the atrioventricular canal across the bulboventricular septum. We have argued that this is not the case, since our evidence indicates that primitive ventricle is a consequence of failure of development of the posterior septum. This process would demand normal *expansion* of the atrioventricular canal in order to form right and left atrioventricular orifices. It can be shown that absence of the posterior septum coupled with *failure of expansion* of the atrioventricular canal, and eccentric fusion of the endocardial cushions and the septum primum would result in formation of hearts with atresia of the right atrioventricular orifice (Fig. 9). Thus, since the posterior septum would be absent, tricuspid atresia could justifiably be considered as a variant of primitive ventricle. Furthermore, it could be expected to exist with or without an outlet chamber. Extending this argument, it follows that straddling right atrioventricular valve cannot be explained on the basis of incomplete migration of the valve to the bulbus. Further evidence in favour of this conclusion comes from the study of Dor and Corone (1973). In their experimental study of the chick heart, they showed that actual *migration* of the atrioventricular canal did not occur. However, their investigation did not rule out the possibility of *expansion* of the canal during development. On our theory, straddling valves can be easily accounted for, since the septum



a) Lack of Expansion

b) Normal Expansion

FIG. 9 *Diagrams illustrating the similarity in morphogenesis between primitive ventricle with two atrioventricular valves and tricuspid atresia. Both can be considered as absence of the posterior interventricular septum and persistence of the bulboventricular septum. Tricuspid atresia results from failure of expansion of the atrioventricular canal together with eccentric fusion of the endocardial cushions. In contrast, primitive ventricle with two valves demands normal expansion of the atrioventricular canal. (B—bulbus; V—primitive ventricle; Ao—aorta; PA—pulmonary artery; TA—tricuspid atresia; PR—posterior ridge.)*

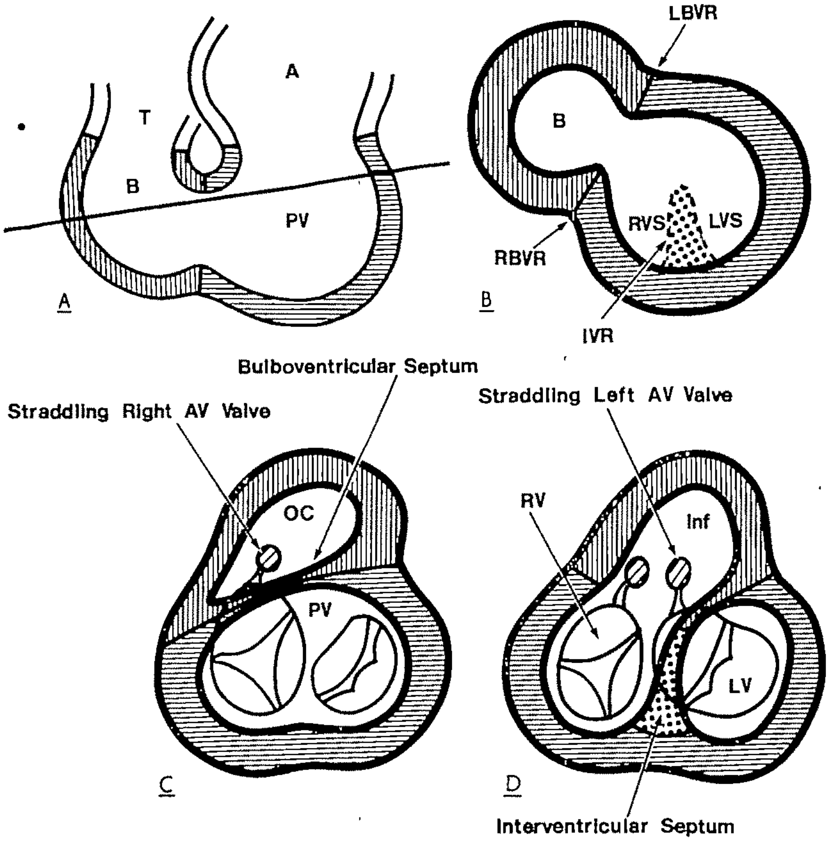


FIG. 10 *Diagrams illustrating the concept of straddling atrioventricular valves. (A) Frontal section through the primitive heart tube (A—primitive atrium; PV—primitive ventricle; B—bulbus; T—truncus). (B) Cross-section at the level of the line. The right and left bulboventricular ridges (RBVR, LBVR) separate bulbus from primitive ventricle. The primitive ventricle itself is divided into the right ventricular sinus (RVS) and left ventricular sinus (LVS) by the interventricular ridge (IVR). (C) Should the bulbus persist as an outlet chamber (OC) with primitive ventricle (PV), then the right atrioventricular valve can straddle the bulboventricular septum. The left atrioventricular valve may also straddle the bulboventricular septum in primitive ventricle with outlet chamber. (D) The mitral valve may also straddle the interventricular septum when right and left ventricles are normally separated (Inf—infundibulum). Reprinted from Shinebourne, Macartney, and Anderson (1976).*

straddled in the case of the right valve would be the *bulbo*ventricular septum rather than the *inter*ventricular septum (Fig. 10). Thus if the anterior papillary muscle arose from the bulbus rather than from the primitive ventricle, in a situation in which the anterior septum was not completely resorbed, then primitive ventricle with outlet chamber and straddling right atrioventricular valve would be formed, as described by Liberthson *et al.* (1971). (Fig. 10).

We, therefore, propose that the univentricular heart is defined as a heart in which the posterior interventricular septum is absent. Such hearts can exist with or without an outlet chamber, with atresia of an atrioventricular orifice, or with a straddling atrioventricular valve. It also follows that the hearts can exist with all possible combinations of atrial chamber morphology and with all possible ventriculo-arterial connexions (Fig. 11). We have thus far studied approximately 200 hearts

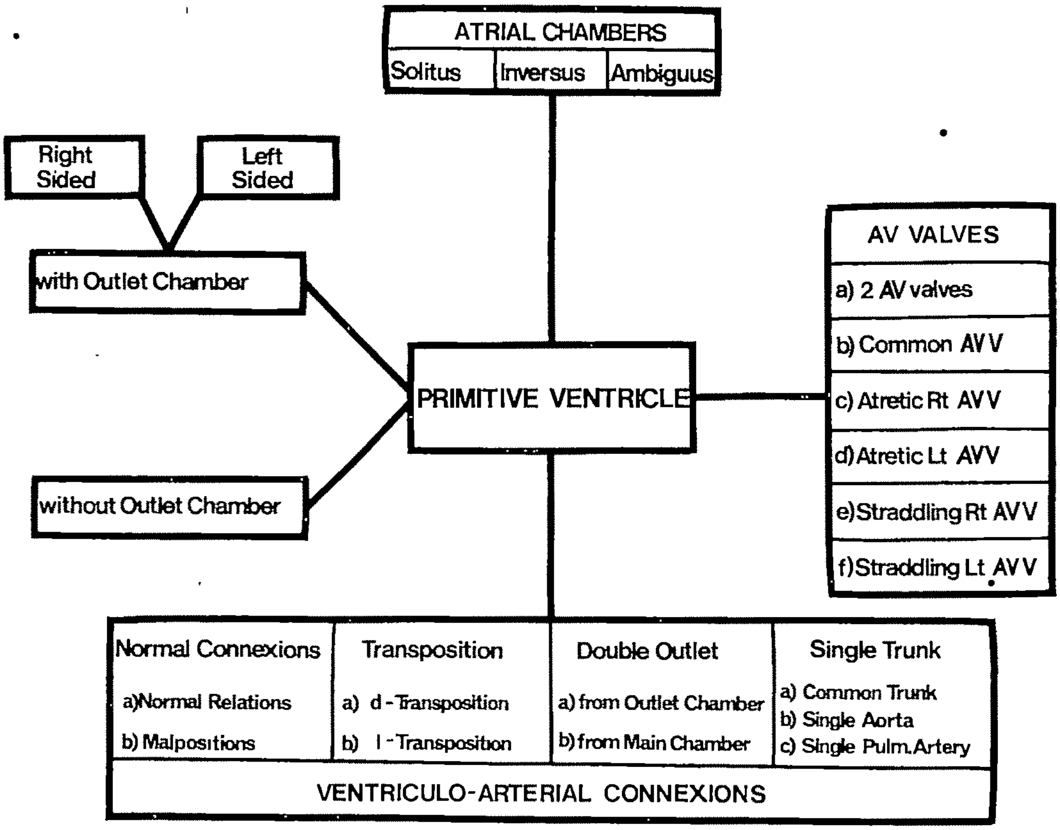


FIG. 11 *Diagram illustrating the possible variations which may be expected in the anomaly of primitive ventricle, defined as absence of the posterior interventricular septum. The scheme is based upon the premises that (a) primitive ventricle can exist with or without an outlet chamber; (b) with any disposition of atrial chambers; (c) with varying malformations of the atrioventricular valves (AVV); (d) with any possible ventriculo-arterial connexion.*

in these categories and the results are in complete agreement with the hypothesis presently advanced. These findings will be published in the near future (R. H. Anderson, A. E. Becker and J. L. Wilkinson, unpublished observations).

We are indebted to Professor O. J. Lewis, Department of Anatomy, St. Bartholomew's Hospital Medical School, for bringing Case 4 to our attention and for his permission to publish this case. We also express our gratitude to Mrs. S. Y. Ho who produced the drawings of this heart.

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Regional pulmonary blood flow in mitral disease studied by xenon radiospirometry

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Regional lung perfusion was measured in the sitting position by 4 external detectors after intravenous injection of ^{133}Xe in 24 patients with mitral valve disease and in 8 people with no cardiopulmonary disease acting as normal controls. Right- and left-sided heart catheterization was carried out on the patients on the following day. Mitral valve stenosis was found in 9, mitral valve regurgitation in 8, and both stenosis and regurgitation in the remaining 7.

Regional lung perfusion in the normal people fell linearly from the basal to the apical sections of the lungs. The perfusion distribution in patients with mitral valve disease and a pulmonary capillary vein (PCV) pressure lower than 15 mmHg (2·0 kPa) did not differ significantly from that of the controls. A redistribution of the regional perfusion, with an increase in the apical perfusion and a fall in the basal perfusion of the lungs, was seen in patients with a raised PCV pressure. The hyperperfusion of the apical lung sections correlated with the mean pressure in the pulmonary artery ($r=+0{\cdot}795$, $P<0{\cdot}001$), while the basal hypoperfusion correlated with the PCV pressure ($r=+0{\cdot}842$, $P<0{\cdot}001$). The PCV pressure can be predicted with an exactitude of ±7 mmHg (0·9 kPa) (95% confidence limits). Neither the cardiac index nor the pulmonary vascular resistance correlated with the changes in perfusion.

Xenon radiospirometry is a rapid and reliable method for evaluating PCV pressure before or after operation in patients with mitral valve disease.

In normal people gravity causes a basal hyperperfusion of the lungs, so that the pulmonary blood flow is greater at the bottom than at the top. Other factors influence the pulmonary blood flow (Jordan, 1965). Basal vascular resistance, measured in the sitting position, decreases when oxygen is breathed (Dawson, Kaneko, and McGregor, 1965) and perivascular oedema (Kazemi *et al.*, 1970) and organic vascular disease can also affect the pulmonary vessels (Olsen, 1966). These factors change the pattern of lung perfusion in patients with mitral valve disease (MVD) (Ball *et al.*, 1962) and may completely invert it.

These perfusion distribution patterns have been studied by means of radioactive gases such as $^{15}O_2$, $^{15}CO_2$ (Dollery and West, 1960), and ^{133}Xe (Ball *et al.*, 1962; Jebavy *et al.*, 1970), and by scanning after the injection of radioactive-labelled albumin aggregate (Friedman and Braunwald, 1966; Giuntini *et al.*, 1974). With ^{133}Xe measurements of regional blood flow can be repeated and expressed in terms of alveolar perfusion. The technique has therefore been used for studying the perfusion distribution in patients with mitral valve disease, and from this, with the patient in the sitting position, a picture of the pressure in the pulmonary circulation may be obtained.

Patients and methods

Twenty-four patients with mitral valve disease were studied. By means of right and left heart catheterization the cardiac output was measured by the method of Fick and also a left ventriculogram taken. Nine of the patients had mitral stenosis, 8 had mitral valve insufficiency, while the remaining 7 had both stenosis and regurgitation. The cardiac catheterization data are shown in the Table.

The patients were subjected to regional radiospirometry the day before heart catheterization. ^{133}Xe dissolved in isotonic saline was injected into a cubital vein of the left arm and the radioactivity in the right lung was measured by 4 scintillation detectors placed posteriorly

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TABLE *Clinical, cardiac catheterization, and lung perfusion data in 24 patients with mitral valve disease*

Case No.	*Age (yr)*	*Sex*	*PCV pressure (mmHg)*	*Mean AP (mmHg)*	*PVR* (*dyn* s^{-1} cm^{-5})	*Cardiac index* (*l* min^{-1} m^{-2})	*Perfusion index (flow/alveolus)**				*Diagnosis*
							1	*2*	*3*	*4*	
1	45	M	3	15	196	2·70	0·546	0·676	1·005	1·330	R
2	58	F	5	16	125	2·10	0·433	0·710	1·150	1·455	R
3	47	F	6	15	176	2·70	0·554	0·794	1·089	1·284	R
4	58	M	8	16	130	2·20	0·622	0·750	1·028	1·269	R
5	64	F	9	16	82	4·34	0·492	0·759	1·061	1·478	R
6	56	F	12	16	84	2·10	0·776	0·930	1·083	1·118	S
7	37	F	14	20	40	4·70	0·714	0·867	1·204	1·073	R
8	53	F	14	20	160	1·80	0·782	0·937	1·109	1·033	S+R
9	37	F	14	21	73	5·10	0·977	1·057	1·015	0·947	R
10	59	F	16	22	55	1·60	0·761	1·000	1·091	1·011	S
11	60	F	16	17	142	1·60	0·960	1·035	1·078	0·920	S
12	49	F	17	25	71	2·70	0·676	0·978	1·050	1·084	S
13	40	M	17	27	144	3·40	0·825	1·113	1·137	0·842	S+R
14	38	F	17	34	384	2·10	0·906	1·062	1·037	0·899	S+R
15	48	F	20	24	35	1·40	0·863	0·964	1·112	0·995	S+R
16	62	M	20	32	180	2·70	0·949	1·010	0·929	1·072	R
17	45	F	21	30	136	2·80	0·907	1·022	0·984	1·021	S+R
18	61	F	22	30	108	2·60	1·266	1·080	0·929	0·771	S
19	51	F	22	29	267	1·30	1·181	1·053	1·093	0·737	S
20	67	M	24	30	138	1·98	1·062	0·957	1·094	0·917	S+R
21	61	F	25	32	175	2·10	1·127	1·353	0·909	0·855	S
22	36	F	25	40	260	2·80	1·291	1·318	0·996	0·625	S
23	46	F	26	32	160	1·90	0·909	1·059	1·083	0·901	S
24	62	F	26	32	88	3·00	1·071	1·149	1·026	0·760	S
Mean	51·7		16·6	24·6	142	2·57	0·860	0·985	1·054	1·016	
±SD	±9·7		±6·9	±7·4	±80	±0·99	±0·237	±0·169	±0·072	±0·221	

*Numbers refer to detectors (see Fig. 1).

PCV=pulmonary capillary venous pressure. AP=aortic pressure. PVR=pulmonary vascular resistance.

S=mitral stenosis. R=mitral regurgitation.

Conversion from Traditional Units to SI Units: 1 mmHg≈0·133 kPa.

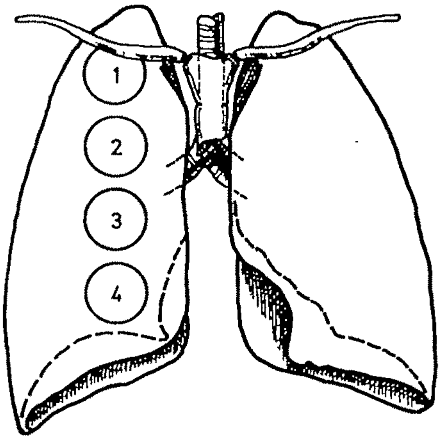

FIG. 1 *Positioning of external scintillation detectors vertically over posterior surface of right lung with 18 cm between centres of upper and lower detector. Internal diameter of each collimator=4 cm.*

vertically above each other (Fig. 1). The upper edge of the apical detector corresponded to a line between the superior margin of the right clavicle and the upper margin of the scapula during maximum inspiration (total lung capacity (TLC)). Perfusion measurements were carried out at TLC, where the difference in perfusion between the top and bottom of the lungs is most pronounced (Anthonisen and Milic-Emili, 1966; Hughes *et al.,* 1968; Lilja, 1972). The detectors had a crystal diameter of 5 cm and a 10-cm long cylindrical collimator. The distance between the centre of the apical and basal detectors was 18 cm in all the investigations. Each detector was connected to a ratemeter with a time constant of 2 seconds and a discrimination level of 81 KeV (Meditronic). The output of the ratemeter was registered on a 4-channel linear writer with a paper speed of 50 mm/s.

After an injection of 0·7 mCi ^{133}Xe the patient inspired to TLC and the breath was then held with the glottis open, in order to eliminate activity from the extrapulmonary circulation (right heart and pulmonary arteries), until the output of the ratemeter reached plateau levels (Fig. 2).

The procedure was repeated three times and the mean

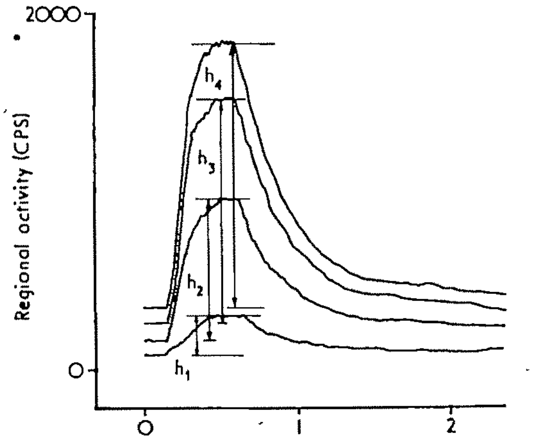

FIG. 2 *Regional ratemeter readings of pulmonary blood flow from 4 detectors in a subject without cardiopulmonary disease recorded at maximum inspiration (TLC). Heights of perfusion h_1, h_2, h_3, and h_4 correspond to detectors 1, 2, 3, and 4 in Fig. 1.*

of the three readings used for the calculations. After this the patient breathed into a closed system consisting of a 5-litre rubber bag full of oxygen connected to a CO_2 absorber. After a stable rebreathing level had been reached the patient inspired again to TLC and continued to do so until the ratemeter output was constant (Fig. 3). At least three measurements were made during inspiration to TLC and the mean regional rebreathing height (Fig. 3) was used for the calculations.

Eight men volunteers, whose mean (±SD) age was

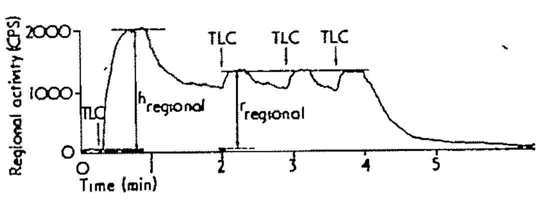

FIG. 3 *Regional ratemeter readings of ^{133}Xe activity on rebreathing into closed system with CO_2 absorber. TLC = plateaus on three inspirations to TLC. $r_{regional}$= expression of amount of alveolar air within field of individual detector.*

21·2±2·0 who had no signs of heart or pulmonary disease and whose lung function was normal were subjected to regional radiospirometry by the same technique as described above. The intra-individual coefficient of variation was within 5 per cent.

Calculations

About 95 per cent of the radioactivity of intravenously injected ^{133}Xe diffuses to the alveolar air during the first passage through the pulmonary circulation (West, 1964). Since ^{133}Xe is uniformly mixed in the right ventricle the amount supplied to each alveolus is proportional to the alveolar blood flow. The height of perfusion 'h' (Fig. 2) is, therefore, proportional to the regional blood flow. Further, the maximum radioactivity registered during breath holding is proportional to the amount of lung tissue within the field covered by the detector and is dependent on the sensitivity of the detector as well as the dose of ^{133}Xe injected. If the perfusion height registered by each detector is expressed as a percentage of the sum of the four perfusion heights then dosage independence is obtained, as follows:

$$h_n\% = h_n \times 100/(h_1+h_2+h_3+h_4)$$

where n = 1, 2, 3, or 4, corresponding to the numbering of the detectors in Fig. 1. If the registered activity of each detector after rebreathing and inspiration to TLC (Fig. 3) is expressed as a percentage of the total rebreathing activity then a dosage independent expression of the amount of lung tissue within the field of each detector is obtained as follows:

$$r_n\% = r_n \times 100/(r_1+r_2+r_3+r_4)$$

where n = 1, 2, 3, or 4.

The ratio (P_n) of the perfusion height in per cent ($h_n\%$) and the rebreathing height in per cent ($r_n\%$) ($h_n\%/r_n\% = P_n$) is therefore dependent only on the regional perfusion. This ratio P_n is termed the perfusion index. Since the size of the alveoli of the apex and base of the lung is the same at maximum inspiration (TLC) (Milic-Emili *et al.*, 1966) r_n per cent is proportional to the number of alveoli, and therefore the perfusion index can be given as flow per alveolus. With increasing perfusion of the apical region the ratio P_1/P_3 will increase and is thus an expression of apical hyperperfusion. Similarly, the expression $P_1+P_2+P_3/P_4$ will increase with decreasing basal perfusion and will thus be an expression of the basal hypoperfusion. These indices of perfusion were chosen being most suitable for correlation with the haemodynamic measurements.

Results

The perfusion indices in the patients with mitral valve disease are shown in the Table and Fig. 4.

In the normal subjects the regional perfusion fell linearly from the base to the apex of the lungs (Fig. 4). A mean bottom/top perfusion ratio (P_4/P_1) of 2·7 was measured. If the 24 patients with mitral valve disease are separated into three according to their PCV pressure the pattern of regional perfusion is significantly different. Apical blood flow increases with increasing PCV pressure while basal perfusion decreases (Fig. 4).

In the 9 patients with mitral valve disease and normal (< 15 mmHg) PCV pressure at rest (group B) the regional perfusion index was not significantly different from that of the normal subjects (group A). The perfusion indices obtained from detector 3

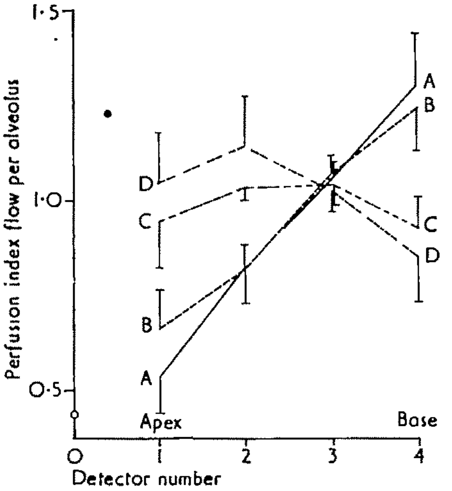

FIG. 4 *Regional perfusion indices (flow/alveolus) at TLC in normal subjects (A) and in patients with mitral valve disease (B, C, D). Group B=9 patients with mean AP 17·2±2·4 (1 SD) mmHg (2·3±0·3 kPa) and PCV=9·4±4·3 mmHg (1·2±0·5 kPa). Group C=10 patients with mean AP 27·0±5·1 mmHg (3·6±0·7 kPa) and PCV=18·8±2·4 mmHg (2·5±0·3 kPa). Group D=5 patients with mean AP 33·2±3·9 mmHg (4·4±0·5 kPa) and PCV=25·2±0·8 mmHg (3·3±0·1 kPa). Increased apical perfusion and decreased basal flow occurs with increasing pressures in pulmonary artery and in PCV. Note: all perfusion indices corresponding to detector 3 are independent of measured pressure. Perfusion indices are given±2 SEM.*

were independent of pressure variations. Apical (P_1/P_3) and basal perfusion ($P_1+P_2+P_3/P_4$) correlated with the pulmonary circulation pressures ($P<0{\cdot}001$).

Regression analysis of the relation between PCV pressure and the basal hypoperfusion enables PCV to be predicted with an exactitude of ±7 mmHg (0·9 kPa) (95% confidence limits). There was no correlation between cardiac output, cardiac index, or pulmonary vascular resistance and perfusion levels.

Discussion

In a person in a sitting position lung perfusion is greatest in the basal region because of the higher hydrostatic pressure. We have measured a bottom-top perfusion ratio of 2·7 in normal subjects. That agrees with the results of other radioactive-gas studies (Dawson *et al.*, 1965; Anthonisen and Milic-Emili, 1966; Lilja, 1972) and scannings after the injection of radioactive labelled albumin aggregate (MAA) (Friedman and Braunwald, 1966).

The mean pressure in the pulmonary artery (PA), measured in cm H_2O, corresponds to the height of the lungs, and for this reason the perfusion pressure is lowest in the apical part. A rise in PA pressure should therefore increase apical perfusion. We confirmed this in our study (Fig. 5). Hypoperfusion of the basal region has been observed with increased PCV pressure (Fig. 6). Such an increase in

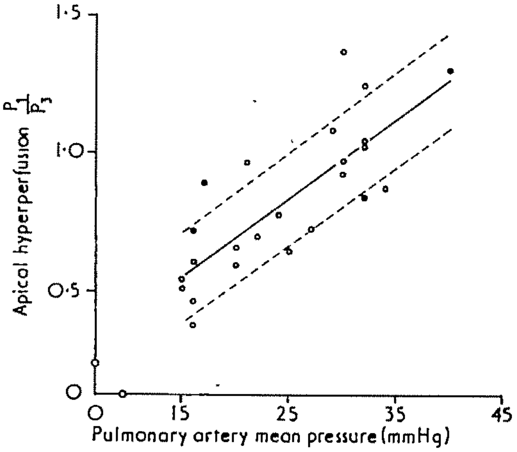

FIG. 5 *Apical hyperperfusion. P_1/P_3 related to mean (±SD) pressure in pulmonary artery in 24 patients with mitral valve disease. Correlation coefficient: $r=+0{\cdot}782$ ($P<0{\cdot}001$).*

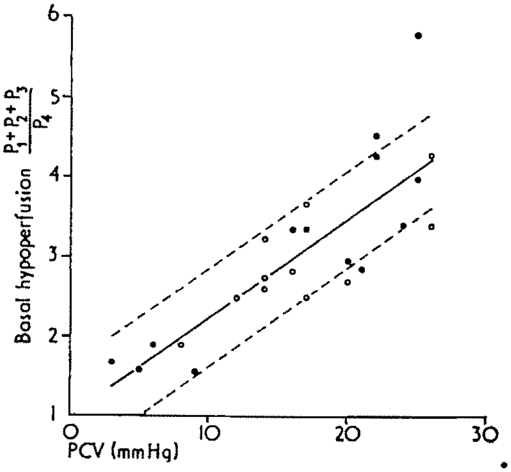

FIG. 6 *Basal hypoperfusion. $P_1+P_2+P_3/P_4$ related to mean (±SD) PCV pressure in 24 patients with mitral valve disease. Correlation coefficient: $r=+0{\cdot}824$ ($P<0{\cdot}001$).*

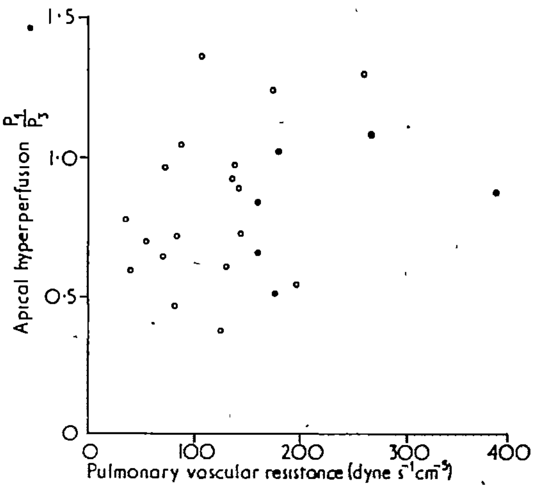

FIG. 7 *Apical hyperperfusion.* P_1/P_3 *related to pulmonary vascular resistance in 24 patients. Correlation coefficient:* $r=+0{\cdot}297$ *(not significant).*

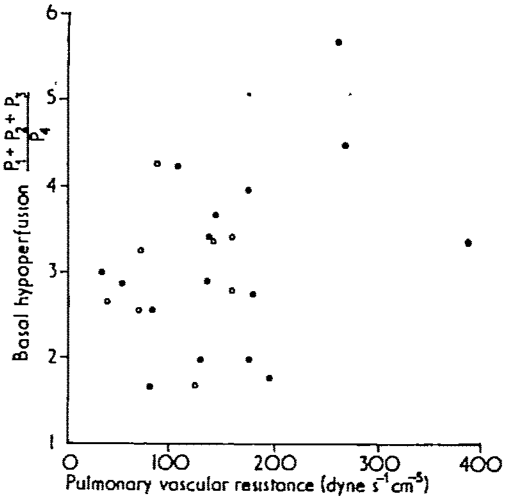

FIG. 8 *Basal hypoperfusion.* $P_1+P_2+P_3/P_4$ *related to pulmonary vascular resistance in 24 patients. Correlation coefficient:* $r=+0{\cdot}340$ *(not significant).*

the basal vascular resistance may be caused by interstitial oedema resulting from a rise in PCV pressure (West, Dollery, and Heard, 1965). Morphological (Olsen, 1966) and functional studies (Steiner, 1958; West *et al.*, 1965) of patients with mitral valve disease (Ball *et al.*, 1962) and of patients with left-sided heart congestion (Kazemi *et al.*, 1970) have confirmed this.

This basal hypoperfusion is partly reversible—as may be seen in patients with mitral valve disease after oxygen treatment (Dawson *et al.*, 1965) and in the decrease in pulmonary vascular resistance after infusion of acetylcholine into the pulmonary artery (Bateman *et al.*, 1962)—whether or not it is caused by the abolition of vasoconstrictive reflexes as a reaction to a raised PCV pressure or by vasoconstriction resulting from hypoxia (McGregor *et al.*, 1953; Dawson *et al.*, 1965; Bergofsky, Haas, and Porcelli, 1968). Normalization of the pulmonary vascular resistance has not been observed either in these studies or in haemodynamic studies after mitral valve surgery (Zener *et al.*, 1972). This is in agreement with the intimal thickening and perivascular fibrosis of the basal vessels found at necropsy in patients with mitral valve disease (Olsen, 1966).

The reduction in basal perfusion that occurs with age first becomes noticeable after the age of 65 (Holland *et al.*, 1968). This is in agreement with the fact that the perfusion distribution in patients with mitral valve disease with normal PA and PCV pressures does not differ significantly from that of normal subjects, despite the difference in average age (Fig. 4).

Friedman and Braunwald (1966) and Giuntini *et al.* (1974) found a positive correlation between pulmonary vascular resistance (PVR) and perfusion distribution in the lungs, but Jebavy *et al.* (1970) and Pain *et al.* (1972) were unable to do so. This correlation is seen only when radioactive MAA has been used. As the resistance of the pulmonary circulation is low compared with that of the systemic circulation an increase in the basal regional resistance, expressed by a reduction in basal perfusion, would not be expected to influence the total PVR. If the patients are grouped according to the upper normal limit of the basal perfusion (mean value of $(P_1+P_2+P_3)/P_4$ (+2 SEM)=2·2) and with normal PVR (<200 dyn s^{-1} cm^{-5}) 80 per cent of the patients with normal PVR have reduced basal perfusion and increased apical perfusion (Fig. 7 and 8) without any increase in PVR. The increase in vascular resistance thus results only in a redistribution of the blood to the apical section.

The PVR in patients above the regression line (Fig. 6) is greater than in patients below it ($P<0{\cdot}02$, *t* test). Thus an increase in PVR is seen simultaneously with a reduction in basal perfusion but independent of the PCV pressure. There must therefore be factors other than the PCV pressure level that bring about the increased PVR. Such a factor could be the effect on the pulmonary blood vessels of a long-standing disease.

The lack of correlation between perfusion distribution and PVR when measured by the ^{133}Xe technique compared with the good correlation found when using radioactive MAA could result from physiological differences in the two methods. Tracer MAA is distributed only to the vascular phase while ^{133}Xe is distributed to both the vascular and air phases. Since ventilation and perfusion are complementary (Liljestrand, 1958) this explanation seems improbable. On the other hand, the discrepancy could result from a difference in the patients studied. Friedman and Braunwald (1966) found no correlation between PVR and perfusion distribution with normal PVR values. This is in agreement with our results. Since a correlation has been found between the results with radioactive MAA and ^{133}Xe used on the same patient (Jebavy *et al.*, 1970) probably the lack of correlation between PVR and perfusion distribution is not due to differences in the methods but is a difference in the patients.

With a raised PCV pressure the mean pulmonary artery (PA) pressure will be correspondingly increased. This will occur up to a PCV pressure of 25 mmHg (3·3 kPa), after which the mean PA pressure increases more than the PCV pressure (excessive pulmonary hypertension (Walston *et al.*, 1973)). All our patients had a PCV pressure of 25 mmHg (3·3 kPa) or less, so that the basal perfusion reduction caused by the moderately increased PCV pressure merely resulted in a redistribution of the blood to the apical lung section with an unchanged PVR. When compensatory changes in the blood flow, which occur at a PCV pressure greater that 25 mmHg (3·3 kPa), become so extensive that they involve the apical section an increase in the PVR and a simultaneous normalization of perfusion distribution can first be observed (Friedman and Braunwald, 1966). The regional pulmonary blood flow can be determined partly by radioactive-labelled MAA (Friedman and Braunwald, 1966) and partly by radioactive gases, for example ^{133}Xe (Ball *et al.*, 1962).

When calculating the regional blood flow the regional count rate must be transformed to flow/ml lung tissue or flow/alveolus. This is done by a geometrical correction, when using the scanning technique, based on measurement of the lung dimensions on the *x*-ray picture of the thorax (Giuntini *et al.*, 1974). With the ^{133}Xe technique the volume correction is simple, since the rebreathing level is an expression of the amount of lung tissue in the fields of each detector. Perfusion measurements may also be repeated when using ^{133}Xe since the radioactivity expires within minutes. The half life of the tracer most often used, ^{131}I-MAA, is three hours (Giuntini *et al.*, 1974), which makes repeated measurements impracticable.

The upper/lower (U/L) perfusion ratio is used in most investigations as an expression of the pulmonary blood flow distribution (Friedman and Braunwald, 1966; Giuntini *et al.*, 1974). U/L will be higher both when the apical perfusion is increased and when the basal perfusion is decreased. We used two distribution ratios, one for apical hyperperfusion (P_1/P_3) and another for basal hypoperfusion ($P_1+P_2+P_3/P_4$). P_2 constitutes part of the expression for the apical perfusion, as this index has been found to be independent of the measured pressure. $P_1+P_2+P_3/P_4$ was used to express the basal hypoperfusion as it gave a better correlation to the PCV pressure ($r=0{\cdot}821$) than was the case with P_3/P_4 ($r=0{\cdot}631$). This discrimination between the apical and basal perfusion is of little importance so long as the PCV pressure is less than 25 mmHg (3·3 kPa) (passive pulmonary hypertension), but this discrimination would be more physiologically correct in cases where the PA pressure increases more than the PCV pressure.

One of the difficulties of quantitatively measuring the regional perfusion distribution is the determination of the basal lung limits. With increased pulmonary venous pressure the range of maximum perfusion is displaced towards the apical region (Hughes *et al.*, 1969), which makes it even more difficult to determine the basal limits. Our four fixed detectors gave a constant hydrostatic pressure difference between the detectors. The volume correction made from the rebreathing level compensated somewhat for the differences in detector positioning in relation to the base of the lung in calculating the relative perfusion. Thus our correlation coefficients were better than those found when there were varying distances between the detectors (for example, U/L) (Dawson *et al.*, 1965; Jebavy *et al.*, 1970; Pain *et al.*, 1972).

Friedman and Braunwald (1966) found a correlation coefficient of 0·91 for the regression between PCV pressure and U/L in 35 patients, despite the fact that small changes in the cardiac output of patients with mitral valve disease may cause considerable fluctuations in the PCV pressure. Our correlation coefficient, $r=0{\cdot}821$, was not significantly different from that found by Friedman and Braunwald (1966) ($P>0{\cdot}05$). The exactitude with which the PCV pressure can be predicted is ±7 mm Hg (0·9 kPa) (95% confidence limits), which is comparable with that of ±5 mmHg (0·7 kPa) (95% confidence limits) found by Friedman and Braunwald (1966). When there are pathological changes in vessel the walls in the lower zones (Olsen, 1966) the perfusion distribution will not be reliable in predicting changes in the left atrial pressure.

Conclusion

The radioactive-xenon method of determining regional pulmonary perfusion in patients with mitral valve disease has been found to be reliable and rapid and may, in contrast to scanning after injection of MAA, be repeated. The volume correction is also simple compared with the scanning technique and the results are immediately available in terms of flow per alveolus. Since it is possible to predict the PCV pressure with an exactitude of ±7 mmHg (0·9 kPa) from the perfusion distribution (95% confidence limits), and since neither extensive intervention nor particular co-operation from the patient are necessary the method can be recommended for the evaluation of patients with suspected mitral valve disease in whom frequent heart catheterization should be avoided—for example, after corrective surgery on the mitral valve.

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Echocardiographic pattern of right atrial tumour motion

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Propagation of Wilm's tumour to the right atrium was diagnosed by echocardiography. The tumour prolapsed into the right ventricle during each atrial systole. The presence of the tumour and its motion were confirmed by cardiac catheterization, cineangiography, and surgical exploration. Successful resection of the tumour was accomplished. Echocardiography was helpful in detecting the presence of the right atrial tumour and accurately reflected the pattern of its atrioventricular motion.

Echocardiography is of established value in the diagnosis of atrial and ventricular cardiac tumours. We wish to report the ultrasonic pattern of a right atrial tumour which prolapsed into the right ventricular outflow tract during each atrial systole. We could find only one report of similar echocardiographic findings in the paediatric age-group (Zajtchuk *et al.*, 1975).

Case report

A 5½-year-old White girl underwent successful removal of Wilm's tumour of the left kidney in November 1974. While on chemotherapy and radiation treatment, a heart murmur was first heard in May 1975. She was referred to us in June 1975. The physical examination showed prominent 'a' waves in the jugular pulses. The praecordium was hyperactive along the left lower sternal border. The first and the second heart sounds were normal. A soft third heart sound was present at the apex and along the lower left sternal border. A grade 2/6, short, early systolic murmur was present along the left sternal border, and radiated toward the pulmonary area. A rough, low pitched, presystolic murmur was present over the left lower sternal border. The liver edge was palpable 6 cm below the right costal margin, and no presystolic pulsations were detectable.

Chest *x*-ray examination showed mild cardiac enlargement and two coin shaped densities in the left lung.

An electrocardiogram indicated right atrial enlargement and right bundle-branch block pattern.

Echocardiography

Ultrasonic examination (Ekoline 20, Cambridge strip chart recorder and 3·5 Megahertz transducer) was diagnostic of a large right atrial tumour, with phasic prolapse into the right ventricular cavity.

The ultrasonic transducer was held in the fourth left intercostal space, about 2 cm lateral to the sternal edge, and the beam was directed inferiorly, leftward, and laterally to record the ventricular septum (VS). In this position a dense layer of echoes was recorded in the right ventricular cavity during right atrial systole (Fig. 1). The beam was then directed medially, rightward, and inferiorly to record the anterior tricuspid leaflet (ATL). In this position, the abnormal, dense layer of echoes was visible throughout the cardiac cycle. During ventricular systole these echoes were seen posterior to the anterior tricuspid leaflet in the right atrial cavity. As the tricuspid valve opened, these tumour echoes prolapsed anteriorly through the tricuspid orifice. The EF slope of the anterior tricuspid leaflet was masked by the tumour echoes.

The ventricular septal motion was flat or type B (Fig. 2A). There were tumour echoes in the right ventricular cavity during ventricular presystole. The left ventricular cavity was clear of any abnormal echoes. Ultrasonic scanning of the aortic root (Fig. 2B) showed that the left atrium and the aorta were normal. Faint but definite tumour echoes were seen in the right ventricular outflow tract during right ventricular presystole.

Course

Cardiac catheterization and biplane cineangiography confirmed the presence of a large right atrial tumour which prolapsed through the tricuspid orifice into the right ventricle and up to the under surface of the pulmonary valve during atrial systole. The tumour was completely contained in the atrial cavity during right ventricular systole. The inferior vena cava was obstructed at the level of the right kidney, and venous drainage

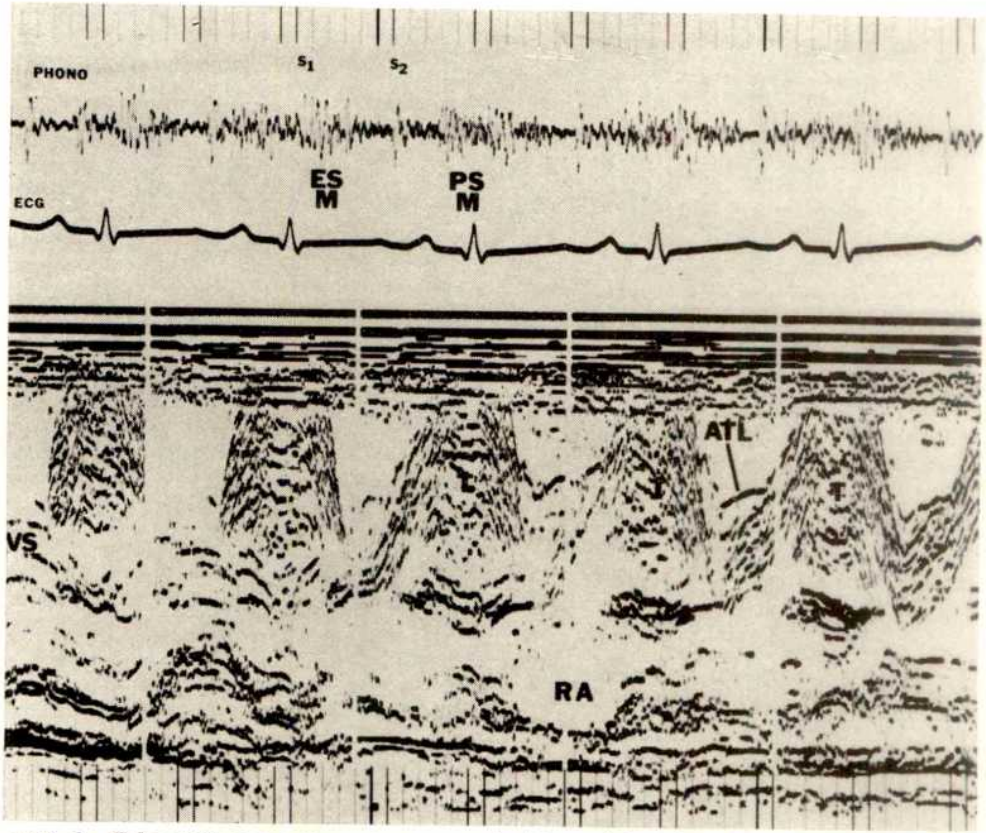

FIG. 1 *Echocardiogram represents a scan of right atrial region. Left side of scan depicts ventricular septum (VS). Then transducer is rotated towards tricuspid region (right side). RA, right atrium; T, tumour; ATL, anterior tricuspid leaflet; phono, phonocardiogram recorded along left lower sternal edge; S_1, first heart sound; S_2, second heart sound; ESM, ejection systolic murmur; PSM, presystolic murmur, ECG, electrocardiogram.*

occurred via the Batson's paravertebral plexus into the azygos and the hemiazygos systems.

Under cardiopulmonary bypass, simultaneous abdominal and cardiac exploration confirmed the clinical diagnosis of intravascular propagation of Wilm's tumour to the right heart. Successful resection of this tumour thrombus was accomplished. The histopathological diagnosis was that of highly malignant nephroblastoma.

The immediate postoperative course was uneventful. Echocardiographic examination (Fig. 3), one week after operation, showed that the tumour echoes were no longer present in the right atrium, right ventricle, and right ventricular outflow tract. The motion of the ventricular septum was normal. The patient was clinically well three months after the operation.

Discussion

Echocardiographic diagnosis of right atrial tumour was made easier by the available history of surgical resection of nephroblastoma six months previously. The echocardiogram was accurate in depicting tumour movement during the cardiac cycle. This ultrasonic study showed that the primary location of the tumour was in the right atrial cavity. Each atrial contraction forced the tumour mass through the tricuspid orifice into the right ventricular outflow tract. This resulted in the presystolic murmur because of the obstruction at the level of the tricuspid valve.

Few reports are available regarding the echocardiographic features of right atrial tumours (Zajtchuk *et al.*, 1975; Harbold and Gau, 1973; Farooki, Henry, and Green, 1975). Approximately six cases of propagation of Wilm's tumour to the right heart have been reported in the English language (Osler, 1879; Anselmi *et al.*, 1970; Edwards, 1972; Murphy *et al.*, 1973; Utley *et al.*, 1973;

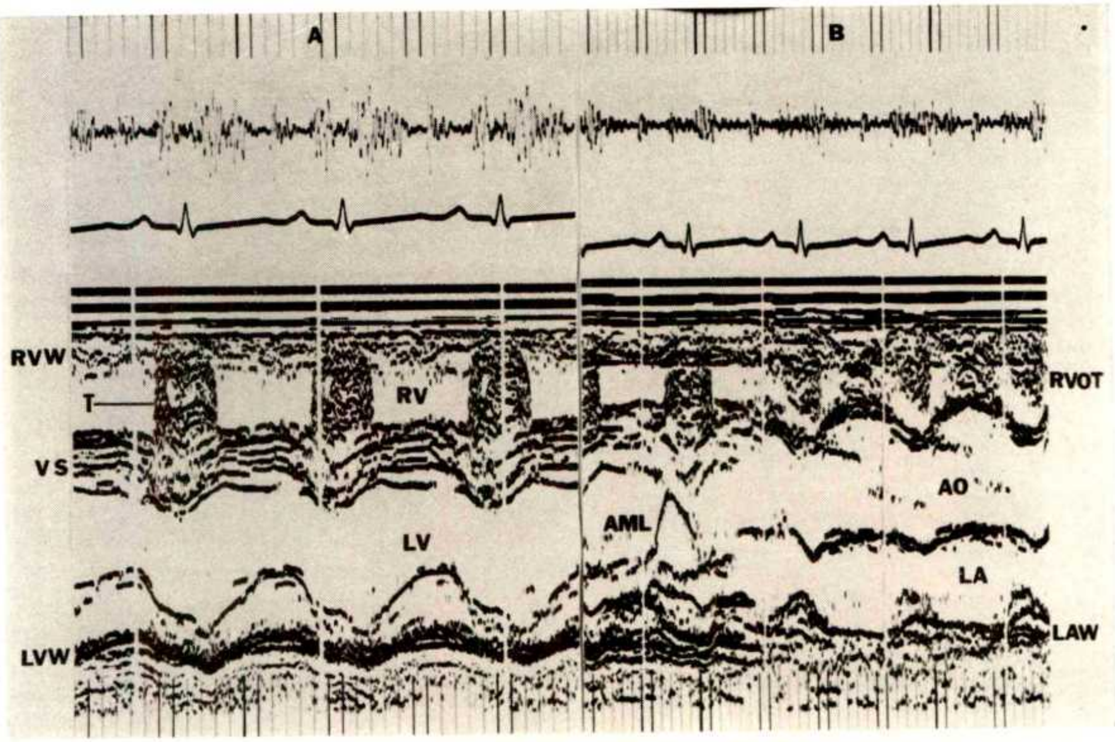

FIG. 2 *Echocardiogram represents scan from left ventricular apex to aortic root. (A) RVW, right ventricular wall; VS, ventricular septum; LVW, left ventricular wall; RV, right ventricle; LV, left ventricle; T, tumour echoes. (B) AML, anterior mitral leaflet; RVOT, right ventricular outflow tract; Ao, aorta; LA, left atrium; LAW, left atrial wall.*

Farooki *et al.*, 1975), and successful removal of the tumour has been accomplished previously (Murphy *et al.*, 1973; Utley *et al.*, 1973).

Echocardiography, as a screening procedure, is recommended for all cases of Wilm's tumour.

The authors are indebted to Dr. Barbara Cushing for referring this patient to us.

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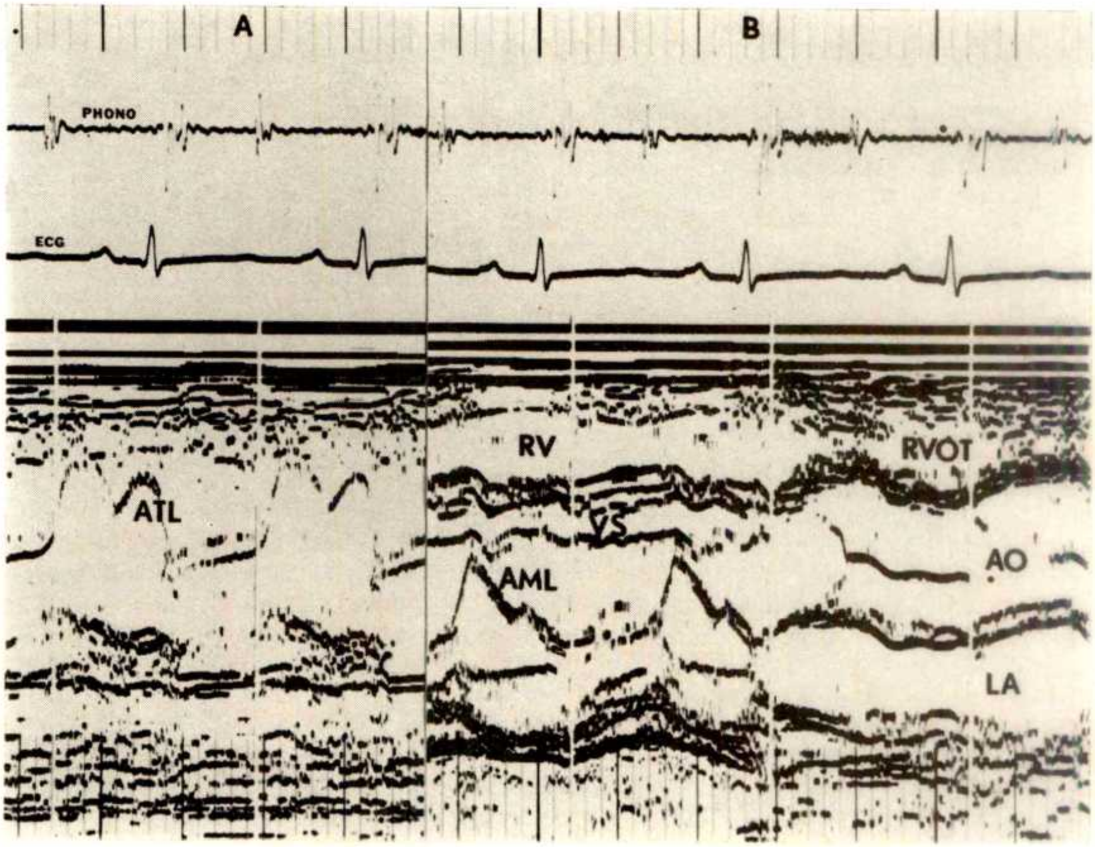

FIG. 3 *Echocardiogram recorded one week after operation. Abbreviations as in Fig. 1 and 2. No tumour echoes are seen.*

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Transposition of great arteries
Early results of Mustard's operation in paediatric patients

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Between May 1969 and June 1975, 43 patients with d-transposition of the great arteries, ranging in age from 2 months to 13 years (mean 19 months), underwent surgical correction. In the first 3 patients Mustard's original method was followed. Later a modified procedure was performed using a Teflon patch. Forty-two of the 43 patients had previously had 50 various palliative procedures, of which 30 were balloon atrial septostomy only. Five patients died in hospital (up to 5 weeks after operation). Of the 32 patients with simple repair of transposition of the great arteries (including 3 with ligation of a persistent ductus arteriosus), 3 died. One patient died as a result of complete AV block, one as a result of renal damage associated with unrelieved coarctation of the aorta, and one of cerebral infarction and peritonitis which probably were initiated preoperatively. Six patients who had additional surgery for pulmonary stenosis survived, including 3 patients who had closure of ventricular septal defect. Of another 5 patients with closure of ventricular septal defect, including 2 who had debanding of the pulmonary artery, 2 died in a low cardiac output state. One infant operated on for subpulmonary stenosis developed permanent complete AV block and was successfully treated with a pacemaker. All the patients with combined operations had some problems postoperatively. The survivors improved greatly, but 2 patients died suddenly one, and one and a half years after the operation respectively.

Haemodynamic correction of transposition of the great arteries by redirecting the pulmonary and the systemic circulation at the atrial level is based on the pioneer work of Albert (1954), of Senning (1959), and of Johansson (1963). Mustard in 1964 described the first case successfully operated upon using a pericardial patch to redirect the caval blood to the mitral orifice and the pulmonary venous blood to the tricuspid ostium. Since then this has become a standard procedure, using either a pericardial or a Dacron patch. Accompanying significant lesions also have to be corrected during the procedure. The present report reviews our experience with this treatment in infants and children.

Procedures

Right-sided thoracotomy was used in the first patients with simple transposition of the great arteries and no previous heart operation. In patients with atrial septal defect after a Blalock-Hanlon procedure, with pulmonary stenosis, or with ventricular septal defect, a sternal split was used, and later this became the standard procedure in all patients. In the first 3 patients we used the original Mustard technique and sutured the patch in front of the coronary sinus. To avoid the region of the atrioventricular node and the bundle of His, in later patients the patch has been placed behind the sinus, draining its blood together with the pulmonary venous blood. In the first 3 patients pericardial patches were used. Later we have used very thin, knitted Teflon (U.S.C.I.[1] No. 3105) because it is pliable, easy to form, and does not stretch.

A standardization of the baffle size and shape according to the patient's weight was worked out, and also the suture line has been somewhat modified (Tjønneland and Hall, 1976). Ventricular septal

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[1] U.S. Catheter+Instrument Corp., Murray Hill, New Jersey 0794, U.S.A.

TABLE 1 *Year of correction*

	1969	*-70*	*-71*	*-72*	*-73*	*-74*	*-June 1975*	*Total No.*
No. of patients	1	2	3	11	16	8	2	43
No. of deaths		1		2	1	1		5

TABLE 4 *Age at correction*

	Months		*Years*			*Total*
	2–6	*7–12*	*1–2*	*3–6*	*7–13*	*No.*
No. of patients	6	6	16	11	4	43
No. of deaths	3			2		5

defects have been closed from the right atrium or from the left ventricle with Teflon patches. Postoperatively, the patients have been ventilated using a naso-tracheal tube for 1 to 2 days, or more if necessary. In the beginning of our series 5 patients had tracheostomies. All patients had continuous monitoring of direct arterial pressure, superior caval venous pressure, and electrocardiogram for a minimum of 1 to 2 days.

Subjects

After only 1 to 3 operations per year in the first years 1969 to 1971 the number reached a peak in 1973, because of an accumulation of patients. The lower number performed in 1974 may represent what is to be the expected annual need for this operation in Norway (Table 1). Before the procedure, 42 of the 43 patients had undergone 50 separate palliative procedures; 30 of the patients had balloon atrial septostomy only (Table 2). Blalock-Hanlon operations were done in 3 patients with an inadequate balloon septostomy, and in 6 patients in a period before the balloon technique was introduced. Two of these had pulmonary stenosis and in them a subclavian-pulmonary anastomosis was performed as well.

All the patients were cyanotic. Most of them also had functional dyspnoea, and some had enlarged livers. The haematocrit was 60 per cent or more in 36 of the 43 patients (Table 3).

The youngest patient was 2 months old and weighed 2·9 kg at the operation. Table 4 shows that 12 of the 43 patients (28%) were operated upon in their first year of life. The mean age of all the patients was 19 months.

Twenty-four patients had transposition of the great arteries and atrial septal defect only. Five patients had additional heart lesions which were not corrected as they were considered to be of minor importance. One was the youngest patient, who had a small persistent ductus arteriosus. Four patients had a mild to moderate pulmonary subvalvar stenosis on the angiocardiogram, with systolic pressure gradients ranging from 28 to 48 mmHg (3·7 to 6·4 kPa) between the left ventricle and the pulmonary artery or wedged pulmonary vein position. One of these also had a moderate coarctation of the aorta.

In 14 of the 43 patients the Mustard procedure was combined with surgery for other heart lesions (Table 5).

TABLE 2 *Palliative procedures before correction*

Type of procedure	*No. of patients*
Balloon atrial septostomy alone	30
Balloon atrial septostomy plus	
Blalock-Hanlon	3
Pulmonary arterial banding	2
Resection of coarctation of aorta plus Pulmonary arterial banding plus Ligation of persistent ductus arteriosus	1
Blalock-Hanlon alone	4
Blalock-Hanlon plus	
Blalock-Taussig anastomosis	2
	42
Medical treatment alone	1

TABLE 3 *Haematocrit values before correction*

Haematocrit (vol. %)	*40–49*	*50–59*	*60–69*	*70–79*	*80–89*	*Total No.*
No. of patients	2	5	19	16	1	43

TABLE 5 *Associated lesions and corrective procedures*

	Total No.	*Deaths*
A. Mustard procedures only	29	3
B. Mustard procedures plus other correction		
Ligation of ductus arteriosus	3	
Pulmonary valvulotomy or subvalvular resection or dilatation*	3	
Closure of ventricular septal defect	3	1
Closure of ventricular septal defect + debanding	2	1
Closure of ventricular septal defect + pulmonary valvulotomy / subvalvular resection	3	
	43	5

*One patient also had a Blalock-Taussig shunt ligated.

TABLE 6 *Early course after correction*

	Simple	*Complex*
Uneventful	24	
Total atrioventricular block	1*	1
Atrial arrhythmias requiring treatment	3	4†
Ventricular fibrillation transient hemiplegia		1
Cardiogenic shock		2*
Bleeding+reoperation	1	
" " +renal failure	1*	
" " +atelectasis	1	
Congestive heart failure		3
Cerebral infarction+peritonitis	1*	
Total no. of patients	32 (3*)	11 (2*)

*Deaths.

†Two patients had also congestive heart failure.

Results

Five (12%) of the 43 patients died. Of the 32 patients (Table 6) who had a *simple Mustard procedure* (including the 3 with ligation of persistent ductus arteriosus) 3 died (9%). One of these developed total AV block with a ventricular rate of 90, which later fell to between 50 and 60 per minute. The use of a pacemaker might have saved him (a later patient in our series, with a combined Mustard procedure and pulmonary valvotomy plus subpulmonary resection also developed total AV block, but is now doing well on a radio-frequency pacemaker). A second patient died of renal failure; he had unrelieved coarctation of the aorta. A 2-month-old infant of 2·9 kg died of cerebral infarction and peritonitis, both of which were probably present before the operation; the clinical assessment was difficult as the patient was very ill, and the final diagnosis was only made at necropsy.

Of the 11 patients who had a *Mustard operation combined with other cardiac surgery*, 2 died (18%), both of low cardiac output after closure of a ventricular septal defect. One was 8 months old and had hyperkinetic pulmonary hypertension. The other was banded at 1 month of age, and the banding was rather tight when he had the Mustard procedure 3½ years later.

Arrhythmias occurred frequently. Besides the total AV block already mentioned, the most serious were repeated episodes of ventricular fibrillation. In one case this occurred on the 4th postoperative day, followed by transient hemiparesis some days later, but with no permanent sequelae. Four patients had atrial flutter and were electrically converted. Another 2 cases had frequent ectopic atrial beats which responded to digitalis. In 3 patients with ventricular septal defect and pulmonary stenosis, severe congestive heart failure developed. They gradually improved on medical treatment.

While 24 of the 32 simple Mustard procedures made an uncomplicated recovery, all the patients with additional heart surgery had some sort of complication.

All the 38 survivors improved considerably, 30 of them being without cardiac symptoms. However, 2 of these died suddenly of no apparent cause one, and one and a half years, respectively, after the operations. Six patients have slight cyanosis clinically, possibly caused by leakage around the baffle. In 11 cases the chest *x*-ray film shows some increase in the heart size; this has occurred more commonly in the patients who have had complex procedures.

Discussion

In the past few years experience with the Mustard operation has been reviewed in a number of reports

TABLE 7 *Results of Mustard's operation for transposition of great arteries (TGA)*

References	*Centre*	*Period in years*	*Total no. of patients (and mortality*)*	*Subgroups (and mortality Simple TGA*
Danielsen *et al.* (1971)	Rochester, Minn., U.S.A.	1964–69	69 (25–*36%*)	25 (3–*12%*)
Waldhausen *et al.* (1971)	Philadelphia, U. S.A.	1965–70	32 (6–*19%*)	18 (0)
Clarkson *et al.* (1972)	Auckland, N.Z.	1965–70	56 (13–*23%*)	46 (7–*15%*)
Breckenridge *et al.* (1972)	London, U.K.	1965–71	200 (36–*18%*)	138 (15–*11%*)
Ihenacho *et al.* (1973)	Birmingham, U.K.	1968–71	37 (10–*27%*)	33 (7–*21%*)
Champsaur *et al.* (1973)	Toronto, Canada	1963–72	123 (26–*21%*)	87 (11–*13%*)
Gutgesell and McNamara (1975)	Houston, U.S.A.	1967–72	31 (8–*26%*)	20 (4–*20%*)
Stafford and McGoon (1973)	Rochester, Minn., U.S.A.	1969–72	31 (4–*13%*)	19 (2–*10%*)
Subramanian (1974)	Buffalo, N.Y., U.S.A.	1969–73	67* (14–*21%*)	34 (3–*9%*)
This series	Oslo, Norway	1969–75	43 (5–*12%*)	32 (3–*9%*)

*All were below 2 years of age and treated under deep hypothermia.

†First figure in parentheses is the number of fatalities, the second figure is the percentage. TGA, transposition of great arteries; I pulmonary stenosis; VSD, ventricular septal defect.

(Table 7). The results reported here compare favourably with the others. In our material the median age was lower and the proportion of complicated cases was about the same as in most of the other series.

Improved results are reported with increased experience. Early mortality in the last year of the series of Breckenridge *et al.* (1972) was only 14 per cent; it was only 15 per cent in the last 2 years of the series of Champsaur *et al.* (1973), and 10 per cent in ours.

Mustard, and most of the other authors, have used pericardium as baffle material. After having tried this first, and then Dacron, Stark *et al.* (1974) went back to pericardium, because caval obstruction occurred with Dacron patches in infants. Stafford and McGoon (1973), however, had no trouble with Dacron. We have used Teflon and we have so far had no clinical problems, but follow-up studies are needed for an adequate evaluation of the baffle.

There is no general agreement yet as to the most suitable age for the Mustard procedure. Waldhausen *et al.* (1971) and Gutgesell and McNamara (1975) prefer the second year of age for transposition of the great arteries with intact ventricular septum, with palliative procedures before that. But the former group have advocated earlier correction if the child's general condition deteriorates. A substantial mortality has been observed however after palliative treatment in the first 12 months of life (Tynan, 1971; Parsons *et al.*, 1971). More recently the trend has been to do early correction, particularly in simple transposition (Aberdeen, 1971). Neutze and Clarkson (1973) reported 2 hospital deaths (11%) after correction of 18 infants with transposition of the great arteries and intact ventricular septum. They now accept 3 months as the optimal age for correction of simple transposition of the great arteries using deep hypothermia. Subramanian (1974) had 2 deaths in 23 infants (9%) and also preferred correction at 3 to 6 months of age. Stark *et al.* (1974), who used routine cardiopulmonary bypass, had only 2 (4%) deaths in their 52 infants with simple transposition of the great arteries.

TGA+PS	*TGA+VSD*	*TGA+PS+VSD*	*Other*
1 (1)	29 (16–55%)	14 (5–36%)	
2 (0)	9 (3–33%)	3 (3)	
—	6 (4)	3 (1)	1 (1)
3 (1)	44 (12–27%)	14 (7–50%)	1 (1)
2 (2)	—	1 (0)	1 (1)
5 (2)	22 (10–45%)	9 (3)	
9 (2)	1 (1)	1 (1)	
2 (0)	7 (1)	3 (1)	
—	21 (4–19%)	12 (7–58%)	
3 (0)	5 (2)	3 (0)	

In our series there were 12 infants, 3 of whom died; of the 9 survivors, 8 had simple transposition of the great arteries and one had resection of a subpulmonary stenosis. Of those who died only one had simple transposition of the great arteries, and his death was unrelated to cardiac surgery. Another died of renal failure, with unrelieved coarctation of the aorta, which possibly should have been repaired before the Mustard procedure. The third had a ventricular septal defect with pulmonary hypertension.

The management of complicated transposition of the great arteries is controversial, the results after the Mustard procedure often being less satisfactory. Those with large or multiple ventricular septal defects, where there may be irreversible pulmonary hypertension, have hitherto first had palliation by banding of the pulmonary artery. This treatment, at 4 to 6 months of age, was still recommended by Bonham-Carter (1973). However, it seems that the current trend is to recommend early primary correction (usually using deep hypothermia). Neutze and Clarkson (1973) found that banding did not give satisfactory palliation. They performed successful primary correction in 4 infants at 2 to 4 months of age, but in another 4 operated upon during the first month of life only 1 survived. Champsaur *et al.* (1973) found that the overall risk of banding with subsequent Mustard procedure, repair of ventricular septal defect, and debanding, was formidable, and also recommended primary correction, before 6 to 8 months of age. Subramanian (1974) had used the same approach in the presence of uncontrolled failure, but was reviewing this policy. Stark *et al.* (1974) used partly deep hypothermia, partly ordinary bypass, in correcting transposition of the great arteries associated with ventricular septal defect (TGA+VSD) with 4 out of 10 infants surviving. Of our 5 patients with TGA+VSD, 2 died, 1 at 3½ years of age (after a banding at 3 months), the other at 8 months of age, with hyperkinetic pulmonary hypertension (and no banding). Our future policy will probably be early primary correction.

Repair of ventricular septal defect and pulmonary stenosis combined with the Mustard procedure has carried a high mortality (Table 7). The procedure of Rastelli (1969) is now recommended (Danielsen *et al.*, 1971; Bonham-Carter, 1973).

Transposition of the great arteries with ventricular septal defect and coarctation or interruption of the aorta poses even more difficult problems. Clarkson *et al.* (1972) had no survivors in this group. Stark *et al.* (1974) stressed the importance of first resecting the coarctation and banding the pulmonary artery, and had patients surviving this procedure awaiting correction. We had one such a patient who survived correction after this initial procedure.

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Serial 3 orthogonal lead electrocardiographic abnormalities after pulmonary embolism
Computer assisted study

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The 3 orthogonal lead electrocardiogram has been evaluated with computer assisted interpretation in 20 patients with acute pulmonary embolism confirmed by pulmonary angiography. Initial 3-lead electrocardiographic abnormalities were found to be at least as helpful as the 12-lead electrocardiogram in supporting the clinical diagnosis. In addition, however, sequential changes in both the maximum QRS and T vector orientations in frontal and transverse planes were more often apparent than any sequential changes in the 12-lead electrocardiogram. While no specific 3 lead electrocardiographic criterion for pulmonary embolism could be determined, this technique was more helpful than conventional methods in following serial electrocardiographic changes in patients with this condition.

The recent availability of pulmonary angiography has facilitated a more critical appraisal of the 12 lead electrocardiographic appearances in acute pulmonary embolism than has hitherto been possible (Stein *et al.*, 1975). As far as is known, there have, however, been no studies to evaluate serial 3 orthogonal lead electrocardiographic abnormalities in patients with acute pulmonary embolism proven angiographically. With the recent availability of a routinely used computer programme for storing orthogonal lead data to enable comment on day-to-day electrocardiographic changes to be made (Macfarlane, Cawood, and Lawrie, 1975), it was decided to undertake a study of 3 orthogonal lead (and corresponding 12 lead) electrocardiograms in order to determine whether or not diagnostic criteria for a positive electrocardiographic change could be incorporated into the routinely used programme.

Subjects and methods

Twenty patients (12 male and 8 female—mean age 52±13) were included in the study. In all cases a diagnosis of acute pulmonary embolism was suspected on clinical grounds and confirmed by pulmonary angiography. Routine clinical investigations were performed in all patients including chest *x*-ray, serial enzyme studies, full blood count and ESR. Patients were divided into two groups for purposes of analysis. Group 1 consisted of 14 patients with no previous history of cardiac or respiratory disease. Group 2 consisted of 6 patients who had a significant cardiac or respiratory history which *per se* had led to the development of an abnormal electrocardiogram. The details of age, sex, duration of symptoms before presentation, together with the underlying diagnosis are shown for groups 1 and 2 in Tables 1 and 2, respectively.

Pulmonary angiography was performed in all cases. A 7×125 Gensini catheter was passed via a right medial cubital vein into right atrium, right ventricle, and then into the main pulmonary artery. Pressure measurements were taken in these three sites. The catheter was then left in the main pulmonary artery and 45 to 55 ml (dose depending on body weight) angiografin were then injected using a Girdlund H-P injector. The angiogram was recorded on 35×35 cm film using an Elema Schonander rapid film changer in conjunction with a high speed fine focus tube. Films were exposed at a rate of 4 per second for 4 seconds and thereafter 1 per second for 9 seconds, allowing dynamic features of the angiogram to be assessed. All patients met one or more of the following major criteria for pulmonary embolism.

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TABLE 1 *Patients with no history of cardiac or respiratory disease (group 1)*

Case No.	*Age*	*Sex*	*Duration of symptoms before presentation (hr)*	*Underlying diagnosis*
1*	48	F	<24	Duodenal ulcer: post vagotomy
2	61	M	<24	Appendicitis: post apppendicectomy
3	77	F	<24	Acute pancreatitis
4	53	M	<48	Thrombophlebitis
5	39	M	<48	Varicose veins: post ligation
6	47	F	<48	Nil
7	62	M	<48	Deep venous thrombosis
8	63	M	<24	Duodenal ulcer: post vagotomy
9	60	M	<24	Varicose veins: post ligation
10	48	M	<24	Varicose veins: post ligation
11	38	F	<48	Fibroids: post hysterectomy
12	42	F	<24	Obesity
13	25	M	<24	Carcinoma of oesophagus
14	71	F	<24	Deep venous thrombosis

TABLE 2 *Patients with positive history of previous cardiac or respiratory disease (group 2)*

Case No.	*Age*	*Sex*	*Duration of symptoms before presentation (hr)*	*Underlying diagnosis*
15	42	M	<24	Atrial fibrillation
16	48	M	<24	Previous myocardial infarction
17	66	M	<24	Previous myocardial infarction
18	57	M	<48	Angina
19	34	F	<24	Rheumatic heart disease
20	62	F	<48	Chondroma right lung; previous resection right middle and lower lobe

(1) Cut-off vessels of large or medium calibre.
(2) Filling defects appearing consistently throughout the arterial phase of the injection.
(3) Vessel loss not related to bullous emphysema.

Patients were subsequently grouped into three categories as follows according to the pulmonary arterial pressure noted during angiography:

(a) Normal: systolic pulmonary artery pressure <30 mmHg (4 kPa).
(b) Moderate pulmonary hypertension: systolic pulmonary artery pressure 30 to 45 mmHg (4 to 6 kPa).
(c) Severe pulmonary hypertension: systolic pulmonary artery pressure >45 mmHg (6 kPa).

The orthogonal lead electrocardiograms (anterolateral lead X, inferior lead Y, and anteroseptal lead Z cf I, aVF, V2) were recorded on each patient using the modified axial lead system (Macfarlane, 1969). Tape recordings were made using a 4-channel FM magnetic tape recorder and the eletrocardiograms were replayed to a PDP8E computer for analysis using a programme which has been described in detail previously (Macfarlane and Lawrie, 1974). Included in the computer print-out were projections of the maximum QRS and T vectors onto the frontal and transverse planes denoted QRS_F, QRS_T, T_F, and T_T, respectively, together with corresponding vector magnitudes.

The following relevant criteria were used for the 3 orthogonal lead electrocardiogram. These have been extracted from the detailed list of diagnostic criteria to be published elsewhere (Macfarlane and Lawrie, 1977) and are presented in simplified form.

(1) RAD: $QRS_F > 65°$.
(2) LAD: $270 < QRS_F < 360°$.
(3) Clockwise cardiac rotation: $180 < QRS_T < 360°$ *and* negative QRS_X area.
(4) LVH: Max QRS vector amplitude $>2{\cdot}5$ mV
or $R_X > 2{\cdot}1$ mV
or $S_Z > 1{\cdot}2$ mV.
(5) RVH: $(R/S)_Z > 3$ *or* $R_Z > 0{\cdot}85$ mV
or ($S_X > 0{\cdot}55$ mV *and* $S_X > R_X$).
(6) Myocardial infarction:
  (a) Inferior: $(Q/R)_Y > 1/3$ *and* $Q_Y > 0{\cdot}03$ s.
  (b) Anteroseptal: $Q_Z > 0{\cdot}02$ s *and* $Q_Z > 0{\cdot}1$ mV
  or ($R_Z < 0{\cdot}10$ mV *and* $(R/S)_Z < 1/10$
  and $180° < 0{\cdot}03$ sec $QRS_T < 330°$).
(7) T wave abnormalities: $T_X < 0{\cdot}05$ mV
or $T_Y < 0{\cdot}05$ mV
or $T_Z < -0{\cdot}05$ mV.

(8) ST abnormalities: Visible ST junctional depression and ST segment flat or downward sloping in any lead.

Sequential changes

(9) T vector: A day-to-day change in T_T or T_F of more than 30°.

(10) QRS vector: A day to day change in $QRS_F >$ 20° or in $QRS_T >$25°.

The normal limits of day-to-day change have been discussed elsewhere (Cawood *et al.,* 1974). If T wave inversion were found to be present in the anteroseptal lead with or without T wave abnormalities in the inferior leads, and if the clinical diagnosis were pulmonary embolism, the computer programme would report T wave changes 'consistent with the clinical diagnosis of pulmonary embolism'.

Twelve lead electrocardiograms were also recorded on each patient using a Siemens direct writing single channel machine. The paper speed was 25 mm/s and the calibration was adjusted such that a 10 mm deflection was equal to 1 mV. The 12 lead electrocardiogram tracing was recorded at the same time as the 3 lead electrocardiogram. The following diagnostic criteria were used in conjunction with interpretation of the 12 lead electrocardiogram by two of the authors. The QRS axis in the frontal plane was determined from Tables (Goldman, 1970).

(1) RAD: Frontal QRS axis >110°.

(2) LAD: Frontal QRS axis <−30°.

(3) Clockwise cardiac rotation: transition line at V5 with S_{V6} present.

(4) RVH: $(R/S)_{V1}>1$ *and* $R_{V1}>$0·7 mV.

(5) S_1 Q_3 T_3: $S_I>$0·15 mV *and* $Q_{III}>$0·15 mV *and* $T_{III}<$0 mV.

(6) LVH: $S_{V1}+R_{V5}>$3·5 mV *or* $R_{aVL}>$1·1 mV *or* $R_{aVF}>$1·5 mV.

(7) Myocardial infarction:
  - (a) Inferior: Q> 0·035 s and Q>1/4 R in any two of II, III, aVF.
  - (b) Anteroseptal: Q>0·20 mV in any two leads V2 to V4 *or* R<0·10 mV in any two leads V2 to V4.

(8) T wave abnormalities: flat or inverted T waves in relevant leads.

(9) ST abnormalities: visible ST junctional depression and ST segment flat or downward sloping in relevant leads.

Sequential T wave changes were diagnosed from 12 lead electrocardiograms in a somewhat subjective

TABLE 3 *Initial 12 and 3 lead electrocardiogram in group 1*

Case No.	*Lead*	*Electrocardiographic changes*	*Pulmonary pressure mmHg*	*kPa*
1	12 3	Normal	35/11	4.7/1·5
2	12	S_1 Q_3 T_3	76/28	10·1/3·7
	3	Q wave in Y lead; LAD		
3	12 3	ST-T changes of inferior ischaemia	50/17	6·7/2·3
4	12 3	ST-T changes of anteroseptal and lateral ischaemia	43/20	5·7/3·7
5	12	ST-T changes of inferior ischaemia	39/11	5·2/1·5
	3	ST-T changes of inferior ischaemia; LAD		
6	12 3	Normal	28/18	3·7/2·4
7	12 3	Left ventricular hypertrophy	56/14	7·5/1·9
8	12 3	Normal	37/12	4·9/1·6
9	12	Normal	26/13	3·5/1·7
	3	LAD		
10	12 3	T wave inversion V1-V3 and in Z lead	27/6	3·6/0·8
11	12 3	T wave inversion in lateral leads	27/9	3·6/1·2
12	12 3	Normal	25/15	3·3/2
13	12	S_1 Q_3 T_3 CCR T wave inversion V1-V3	50/15	6·7/2
	3	T wave inversion Z lead, CCR, RAD		
14	12	S_1 Q_3 T_3 CCR T wave inversion V1-V3	52/14	6·9/1·9
	3	T wave inversion Z lead, RAD, CCR		

LAD, left axis deviation; RAD, right axis deviation; CCR, clockwise cardiac rotation.

manner by the two reviewers on the basis of the appearance of fresh T wave inversion or increase in inverted T wave amplitudes. Sequential QRS axis changes could not be reported as no known criteria were available.

Three and 12 lead electrocardiograms were recorded from almost all patients on at least 3 occasions, including the time of presentation, which was always less than 48 hours from the onset of symptoms, and the day of pulmonary angiography.

Results

Group 1

The main features of the initial 3 and 12 lead electrocardiograms together with pulmonary artery pressure are shown for each patient in Table 3. Three and 12 lead findings were the same in 9 patients while all patients were in sinus rhythm. Table 4 summarizes the frequency of selected electrocardiographic measurements.

Table 5 presents the sequential electrocardiographic abnormalities detected in group 1 patients. Sequential changes in either the QRS or T vectors were present in 8 patients according to 3 lead diagnostic criteria while sequential T wave changes in the 12 lead electrocardiograms were noted in 6 patients. QRS vector angles in the frontal and transverse planes are shown where an abnormal shift has occurred or where the vector has moved from a normal to an abnormal orientation.

Pulmonary artery pressure was normal in 5 patients in this group, moderately raised in 4 patients, and severely raised in 5. All three patients with S_1 Q_3 T_3 had severe pulmonary hypertension as had the two patients with marked QRS_F vector shifts detected by the 3 lead electrocardiogram.

Group 2

Three and 12 lead electrocardiogram results in group 2 patients are summarized in Table 6. There was no difference between initial 3 and 12 lead reports, but five patients subsequently showed significant QRS or T vector changes on the 3 lead electrocardiogram whereas in only one patient were sequential changes noted by the 12 lead electrocardiogram. Two patients in this group had no pulmonary hypertension, 2 had moderate pulmonary hypertension, and the remaining 2 had severe pulmonary hypertension.

TABLE 4 *Summary of 3 and 12 lead appearances, group 1*

	3-lead	*12-lead*
Sinus tachycardia	5	5
Atrial ectopics	2	2
S_1 Q_3 T_3	0	3
T wave inverted anteroseptal leads	3	3
Left axis deviation	3	0
Right axis deviation	2	0
Clockwise cardiac rotation	2	2

TABLE 5 *Sequential changes in group 1*

Case No.		*T wave*	*Frontal*	*QRS Transverse*
2	12	+ve	–ve	–ve
	3	+ve		
3	12	+ve	–ve	–ve
	3	+ve		
9	12	–ve	–ve	–ve
	3	+ve		
10	12	+ve	–ve	–ve
	3	+ve		
11	12	–ve	–ve	–ve
	3	+ve		
12	12	–ve	8→ 26→ 72	331→ 291→ 340
	3	–ve		
13	12	+ve	268→ 190	262→ 209
	3	+ve		
14	12	+ve	182→ 163→ 136	223→ 225→ 237
	3	+ve		

Discussion

Twelve lead electrocardiographic appearances after acute pulmonary embolism have been well documented. Few of these are diagnostic of pulmonary embolism though the S_1 Q_3 T_3 pattern (McGinn and White, 1935) and T wave inversion in the right praecordial leads (Sutton, Honey, and Gibson, 1969) are helpful confirmatory findings. The former is more likely to be present when there is major pulmonary vascular obstruction with pulmonary hypertension but even then this abnormality may not occur (McIntyre, Sasahara, and Littmann, 1972), and the latter appears to be particularly associated with acute massive pulmonary embolism (Sutton *et al.*, 1969). In the 3 patients in this study with S_1 Q_3 T_3, the 3 lead electrocardiogram did not show a specific abnormality with which this pattern could be equated but nevertheless showed striking right axis deviation in two, with a Q_Y S_X pattern in the third. In respect of 5 of 20 patients with T wave abnormalities in the right praecordial leads V1 to V3, the computer interpretation of the 3 lead electrocardiogram also noted anteroseptal T wave abnormalities and commented on their relevance to the clinical diagnosis of pulmonary embolism. Three of these patients had significant haemodynamic changes, one had

TABLE 6 *Electrocardiographic findings in group 2*

Case No.		*Initial*	*Sequential changes* *T Wave*		*QRS* *Frcntal*	*Transverse*	*Pulmonary artery pressure* *mmHg*	*kPa*
15	3	Atrial fibrillation	3	+ve	18→7→48	324→294→274	25/18	3·3/2·4
	12	Inferior myocardial ischaemia	12	−ve	−ve	−ve		
16	3	Sinus rhythm; LAD	3	−ve	−ve	−ve	43/23	5·7/3·1
	12	Anteroseptal myocardial infarction	12	−ve	−ve	−ve		
17	3	Sinus rhythm, LAD	3	+ve	−ve	−ve	24/10	3·2/1·3
	12	Inferior myocardial infarction	12	−ve	−ve	−ve		
18	3	Sinus rhythm	3	+ve	−ve	−ve	45/17	6·0/2·3
	12	Widespread myocardial ischaemia	12	−ve	−ve	−ve		
19	3	Sinus rhythm	3	+ve	47→70→58	344→304→337	66/26	8·8/3·5
	12	T wave inversion in anteroseptal leads	12	+ve	−ve	−ve		
20	3	Atrial fibrillation; RAD	3	−ve	156→119→76	178→239→231	84/55	11·2/7·3
	12	Clockwise cardiac rotation	12	−ve	−ve	−ve		

moderately raised pulmonary artery pressure and one had normal pressure. Sequential T wave changes in group 1 were detected in 7 patients by the 3 lead electrocardiogram and in 5 patients by the 12 lead electrocardiogram. In group 2, it was extremely difficult to infer any relation between T wave changes and acute pulmonary embolism, but 3 out of 6 patients showed sequential T vector changes in the 3 lead electrocardiogram whereas no sequential T wave changes were evident on the 12 lead electrocardiogram.

The diagnosis of QRS axis shifts can be accurately estimated in the 3 lead system and an abnormality of the frontal or transverse maximum QRS vector occurred at some stage in 11 of 20 (55%) patients. All patients with initial right axis deviation showed subsequent abnormal QRS vector shifts and a further 3 showed significant sequential QRS vector shifts. Left axis deviation was noted on at least one occasion in 5 of 20 (25%) patients, in keeping with the findings of Lynch, Stein, and Bruce (1972) who reported that left axis deviation was twice as common as right axis deviation in patients with acute pulmonary embolism.

Clockwise cardiac rotation is known to be associated with acute pulmonary embolism (Cutforth and Oram, 1958; Phillips and Levine, 1950). All of the 3 patients with clockwise cardiac rotation in our series retained this abnormality throughout the period of the study, though the QRS_T vector rotated clockwise while the QRS_F vector correspondingly rotated in an anticlockwise direction as the time from the initial incident increased.

The temporal relation of electrocardiographic changes and acute pulmonary embolism is of great importance, and Spodick (1972) has emphasized the value of establishing a relation between likely time of the acute embolism and the initial electrocardiogram. In this study 13 patients (65%) had tracings recorded within 24 hours of initial symptoms while the remaining 7 patients had their first electrocardiogram recorded within 48 hours.

There was no specific 3 orthogonal lead electrocardiographic pattern which could be said to be typical of pulmonary embolism. Classical signs such as T wave inversion in the anteroseptal lead appeared simultaneously in both lead systems but could not be regarded as pathognomonic of pulmonary embolism. Likewise while significant QRS vector shifts outside normal day-to-day variation occurred in 6 of 20 (30%) patients, there was no pattern to suggest that one direction of rotation was prevalent. This is in keeping with findings of right and left axis deviation in patients with pulmonary embolism. Thus, there was no diagnostic criterion which could be regarded as a definite indication of pulmonary embolism.

Although there are additional difficulties in the assessment of electrocardiographic changes in patients with previously abnormal tracings, the exact effect of previous cardiopulmonary disease is not certain. It has been suggested, both in animals (Just-Viera *et al.*, 1965) and in man (Szucs *et al.*, 1971), that the incidence of electrocardiographic abnormalities may not be altered. It seems that the important factor in this situation is the demonstration of a changing electrocardiogram in the presence of a known pre-existing abnormality. We have found that in 5 out of 6 patients with known cardiac or respiratory disease, sequential 3 lead electrocardiographic changes occurred. In only one patient were definite sequential changes noted on the 12 lead tracings. These findings suggest that serial 3 lead tracings in this type of patient with suspected pulmonary embolism are of more value in supporting the diagnosis than the 12 lead electrocardiogram.

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B-scan ultrasonography in idiopathic hypertrophic subaortic stenosis[1]

Study of left ventricular outflow tract and mechanism of obstruction

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Studies were made with standard time motion and B-scan echocardiography on 48 patients including 5 with idiopathic hypertrophic subaortic stenosis (hypertrophic obstructive cardiomyopathy), undergoing diagnostic cardiac catheterization. The dimensions of the left ventricular outflow (O) and inflow (I) tracts were measured on the B-scan images. The outflow tract was significantly narrowed in idiopathic hypertrophic subaortic stenosis at both end-systole (1·1±0·1 cm) and end-diastole (1·3±0·1 cm) when compared with the average width in other patients (2·6±0·1 and 3·0±0·1 cm, at end-systole and end-diastole, respectively) ($P<0{\cdot}001$) or normal subjects (2·4±0·3 and 2·9±0·2 cm) ($P<0{\cdot}01$). Furthermore, the O/I ratio differed significantly in idiopathic hypertrophic subaortic stenosis (0·5±0·1 at end-systole and 0·6±0·1 at end-diastole) from that in all other groups (1·4±0·1 at both end-systole and end-diastole) ($P<0{\cdot}005$). There was no appreciable change in the width of the outflow tract from mid- to end-systole in the two patients in whom this was examined. The data support the contention that the anterior leaflet of the mitral valve assumes an abnormally anterior position *in idiopathic hypertrophic subaortic stenosis. Though the systolic anterior* movement *of the tip of the anterior leaflet of the mitral valve shown by M-mode echocardiography could not readily be confirmed with B-scans, we believe that the narrowed outflow tract found in the present investigation contributes to the obstruction that occurs in this disease. We suggest that this outflow tract narrowing is probably caused by hypertrophy of the ventricular septum which in itself contributes to the narrowing, but which also displaces the papillary muscles and thus produces abnormal traction on the mitral valve and striking anterior displacement of the valve apparatus.*

Idiopathic hypertrophic subaortic stenosis (hypertrophic obstructive cardiomyopathy) is a familial condition (Clark, Henry, and Epstein, 1973) which results in varying degrees of obstruction of the left ventricular outflow tract. Recent haemodynamic (Brockenbrough, Braunwald, and Morrow, 1961; Braunwald and Ebert, 1962; Krasnow *et al.*, 1963; Pierce, Morrow, and Braunwald, 1964) and angiographic (Dinsmore, Sanders, and Harthorne, 1966; Simon, Ross, and Gault, 1967; Adelman *et al.*, 1969; Simon, 1972) studies have defined the dynamic nature of this obstruction. Throughout the cardiac cycle the asymmetrically hypertrophied interventricular septum significantly narrows the outflow tract. Abnormal angulation of papillary muscles prevents the anterior mitral leaflet from normally swinging posteriorly at end-diastole, thus further compromising the outflow tract at the onset of systole (Simon *et al.*, 1967). Alteration of the outflow tract size and resulting pressure gradient by numerous pharmacological agents and physiological interventions attests to the dynamic nature of this obstruction (Brockenbrough *et al.*, 1961; Braunwald and Ebert, 1962; Krasnow *et al.*, 1963). The introduction of ultrasound techniques has greatly simplified the diagnosis of this disorder and has helped explain its pathophysiology. Asymmetric

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septal hypertrophy (Pridie, Behnam, and Wild, 1972; Henry, Clark, and Epstein, 1973a; Epstein *et al.*, 1974) and early systolic anterior movement of the anterior mitral leaflet (Popp and Harrison, 1969; Shah, Gramiak, and Kramer, 1969; Shah *et al.*, 1971; Pridie *et al.*, 1972; Henry *et al.*, 1973b; King *et al.*, 1973a; Epstein *et al.*, 1974) are the echocardiographic abnormalities which have been demonstrated in idiopathic hypertrophic subaortic stenosis. Not well appreciated is the evidence from echocardiography of narrowing of the outflow tract in *both* systole and diastole caused by the relatively fixed abnormal anterior displacement of the mitral valve apparatus (Gramiak, Shah, and Kramer, 1969; Moreyra *et al.*, 1969; Popp and Harrison, 1969; Shah *et al.*, 1969; Gramiak and Shah, 1971; Shah *et al.*, 1971; Abbasi *et al.*, 1972; Feigenbaum, 1972; Pridie *et al.*, 1972; Shah *et al.*, 1972; Henry *et al.*, 1973b; King *et al.*, 1973a: Williams, Ellison, and Nadas, 1973; Epstein *et al.*, 1974; Henry *et al.*, 1975). This narrowing can best be defined by an ultrasound technique which scans the entire length of the outflow tract. The use of this technique forms the basis of the present report.

Subjects and methods

Five patients (2 males, 3 females) with idiopathic hypertrophic subaortic stenosis were evaluated with both standard M-mode and B-scanning echocardiographic techniques. Examinations were performed less than 24 hours before diagnostic cardiac catheterization in all but one patient whose catheterization was 13 months before the ultrasound study. The diagnosis of idiopathic hypertrophic subaortic stenosis was confirmed by the finding of characteristic haemodynamic abnormalities either at rest or after inotropic stimulation (Braunwald *et al.*, 1964). Of the additional 43 patients (36 men, 7 women) studied in a similar fashion, 26 had coronary artery disease and 3 of these had coexistent mitral regurgitation. Six patients had primary valvular disease (aortic stenosis 2, aortic regurgitation 1, mitral stenosis 2, mitral regurgitation 1). An additional 4 patients had left-to-right shunts (atrial septal defect 3, ventricular septal defect 1), and 7 were normal.

The technique for performing the ultrasound studies has previously been described (Teichholz *et al.*, 1974). Briefly, standard echocardiographic recordings as well as B-scans were made in all patients using a Unirad Sonograf and a 2·25 MHz transducer placed in either the third, fourth, or fifth intercostal space. The ultrasonic 'B' mode display was presented on a Tektronix storage oscilloscope and photographed with a Polaroid camera. A gate triggered by the patient's electrocardiogram was used to produce stop-action, two-dimensional cross-sectional images of the heart at end-systole and end-diastole. As previously explained (Teichholz *et al.*, 1974), the peak of the R wave was chosen as end-diastole and the D point of the mitral valve echogram as end-systole. The plane of the scanning arm was adjusted to pass through the aortic root, anterior leaflet of the mitral valve, interventricular septum, left ventricular posterior wall, and cardiac apex. The transducer was slowly moved along the chest wall, and portions of the left ventricular silhouette were developed at each point by sector scanning. In this manner a complete silhouette could be formed on a storage oscilloscope and subsequently photographed. Spatial orientation of all structures recorded in the silhouettes was possible by simultaneously observing an A-mode display and photographing a time-motion echogram on a strip-chart recorder while the scans were being formed. 1 cm interval markers were recorded in each photograph to allow measurement of absolute dimensions.

Only left ventricular silhouettes clearly showing the anterior leaflet of the mitral valve were analysed. Because of the rapid movement of the tip of this leaflet, it was not always possible to record its motion in the scan, and therefore measurements have been made to the mid-portion of the visualized leaflet, at least 1 cm below the mitral ring. The distance between the anterior leaflet and the base of the posterior left ventricular wall immediately distal to the atrioventricular junction was taken to represent the inflow tract (I) (Fig. 1). The left ventricular outflow tract (O) was measured as the distance between the leaflet and the base of the septum immediately caudad to the aortic root or bulging superior portion of the interventricular septum in those patients where this was apparent. These measurements were made directly from the scan photographs in both end-systole and end-diastole. The ratio O/I was calculated in both phases of the cardiac cycle.

Results are presented as mean values ± standard error of the mean.

Results

A B-scan from a patient with coronary artery disease is presented in Fig. 1. This scan shows the normal position of the anterior leaflet of the mitral valve at end-systole. In this patient O=2·6 cm, I=2·5 cm, and O/I is 1·04. By contrast, Fig. 2 represents an end-systolic left ventricular silhouette

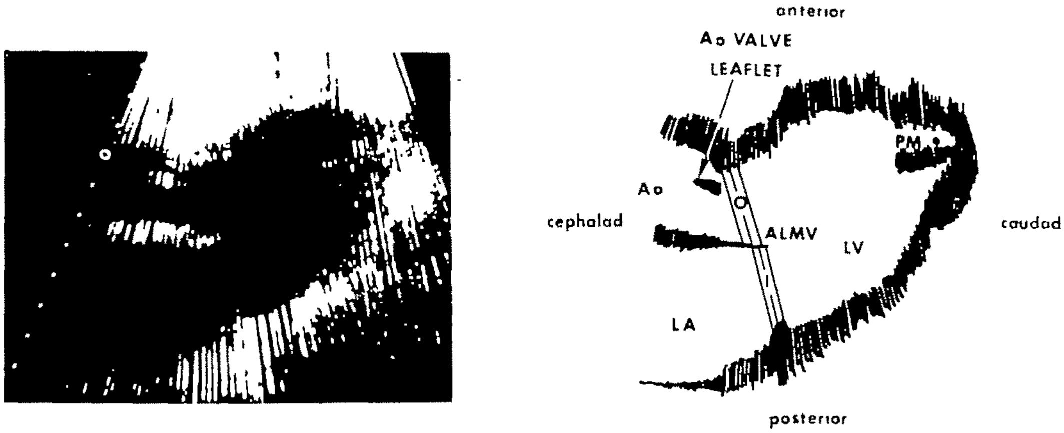

FIG. 1 *Photograph (left) and artist's sketch (right) of an end-systolic B-scan from a patient with two-vessel coronary artery disease. The anterior leaflet of the mitral valve (ALMV) is normally positioned. The outflow tract (O) measures 2·6 cm and the inflow tract (I) 2·5 cm, while the O/I ratio is 1·04. The distance between the interval markers on the photograph represents 1 cm.*
Abbreviations: PM=papillary muscle, Ao=aorta, LA=left atrium, LV=left ventricle.

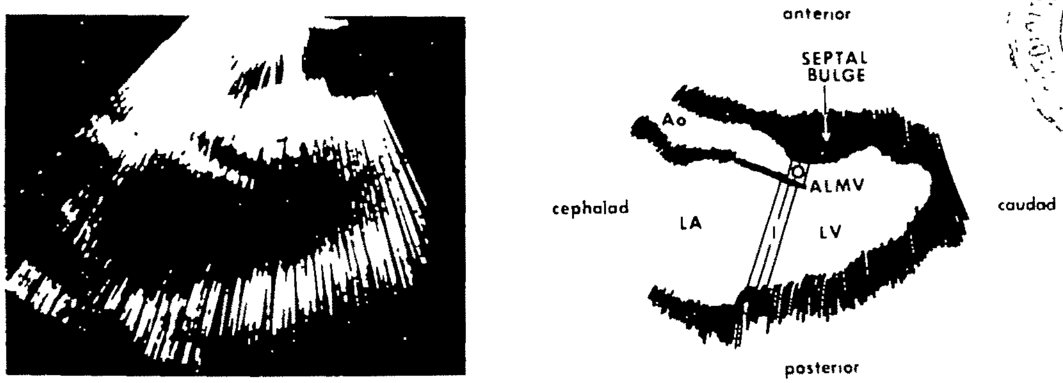

FIG. 2 *Photograph (left) and artist's sketch (right) of an end-systolic B-scan from a patient (Case 3) with idiopathic hypertrophic subaortic stenosis and a 60 mmHg (8·0 kPa) gradient between left ventricle and aorta at rest. The anterior leaflet of the mitral valve (ALMV) is anteriorly displaced and is separated from the prominent septal bulge by only 0·9 cm, thus significantly narrowing the outflow tract (O). The width of the inflow tract (I) is 3·7 cm and the O/I ratio is 0·24. The distance between the interval markers on the photograph represents 1 cm.*
Abbreviations: see Fig. 1.

in a patient (Case 3) with idiopathic hypertrophic subaortic stenosis. In this patient the resting outflow tract gradient was 60 mmHg (8·0 kPa). The anterior leaflet of the mitral valve is displaced anteriorly, producing significant narrowing of the left ventricular outflow tract during systole: O=0·9 cm, I=3·7 cm, and O/I=0·24. The data for individual patients with idiopathic hypertrophic subaortic stenosis are presented in Table 1, and the results for all patients are tabulated in Table 2 and presented graphically in Fig. 3. There was obvious difference in the individual O/I ratios in all patient groups compared with those in the 4 patients with idiopathic hypertrophic subaortic stenosis with gradients either at rest or after spontaneous premature ventricular contractions. In these latter patients O averaged 1·1 cm (range 0·9 to 1·3) at end-systole and 1·2 cm (range 0·9 to 1·5) at end-diastole with average O/I ratios of 0·38 (range 0·24 to 0·48) in systole and 0·44 (range 0·24 to 0·75) in diastole. By contrast, no patient with a cardiac diagnosis other than idiopathic hypertrophic subaortic stenosis had an outflow tract smaller than 1·5 cm at either end-systole or end-diastole. Only one subject without idiopathic hypertrophic subaortic stenosis had an O/I ratio less than 0·75 in either the end-systolic or end-diastolic scan. One patient with idiopathic hypertrophic subaortic stenosis had an outflow tract gradient seen only after isoprenaline infusion. This patient had a narrow outflow tract (1·3 cm in systole and 1·4 cm in diastole), though the O/I ratios were in the normal range (0·93 in systole and 1·00 in diastole).

TABLE 1 *Echocardiographic, angiographic, and haemodynamic data in patients with idiopathic hypertrophic subaortic stenosis*

Case No.	*Date of cath.*	*Age*	*Echocardiography TM-mode*		*B-scan*				*Mitral regurgitation*	*Left ventriculo-aortic pressure gradient (mmHg)*		
			SAM of MV anterior leaflet	*MV anterior position*		*O (cm)*	*I (cm)*	*O/I*		*Rest*	*Post-ectopic*	*Isoprenaline*
1	20/4/72	30	Yes	Yes	S	1·3	3·5	0·37	0	77	—	—
					D	1·5	3·5	0·42				
2	17/1/73	22	No	No	S	1·3	1·4	0·93	0	0	0	40–60
					D	1·4	1·4	1·00				
3	18/1/73	31	Yes	Yes	S	0·9	3·7	0·24	++	60	100	—
					D	0·9	3·7	0·24				
4	24/1/73	53	Yes	Yes	S	1·1	2·5	0·44	0	0	60	35
					D	1·5	2·0	0·75				
5	17/10/73	53	Yes	Yes	S	1·1	2·3	0·48	0	20	100	—
					D	1·1	3·0	0·37				

Abbreviations: Cath.=catheterization procedure; MV=mitral valve; O=width of left ventricular outflow tract; I=width of left ventricular inflow tract; Post-ectopic=beat following premature ventricular contraction; S=end-systole; D=end-diastole; SAM=systolic anterior movement.

In 2 patients with documented idiopathic hypertrophic subaortic stenosis and resting gradients a B-scan was also recorded at a time in mid-systole when the systolic anterior movement of the anterior mitral leaflet as seen in the standard echocardiogram was maximal. O, I, and O/I measurements at this time were identical to those measured at end-systole.

Discussion

B-scan ultrasonography uses echocardiographic techniques to generate conventional two-dimensional silhouettes of the left ventricle. These silhouettes illustrate geometrical relations between cardiac structures better than the standard time-motion display, though the latter provides better resolution of rapidly moving structures. The present study has used left ventricular B-scans to document the abnormal anterior position of the anterior mitral leaflet in idiopathic hypertrophic subaortic stenosis which may contribute to the outflow tract obstruction observed in this disorder.

Left ventricular angiographic studies have been invaluable for the understanding of the pathophysiology of idiopathic hypertrophic subaortic stenosis by showing an anatomical basis for the functional obstruction of the outflow tract (Dinsmore *et al.*, 1966; Simon *et al.*, 1967; Adelman *et al.*, 1969; Simon, 1972). The outflow tract is normally bounded by the interventricular septum anteriorly and laterally and the anterior mitral leaflet posteriorly. With asymmetrical hypertrophy of the muscular septum, there is direct encroachment of this muscle mass on the anterior part of the left ventricular outlet. The mid-superior portion of this hypertrophied septum projects into the ventricular cavity thus displacing the anterior papillary muscle anteriorly, superiorly, and medially away from the major longitudinal axis of the left ventricle (King *et al.*, 1973b; Reis *et al.*, 1974). This unusual angulation of the papillary muscle coupled with the lack of apex-to-base shortening, because of the massive septal hypertrophy (Klein, Lane, and Gorlin, 1965), produces abnormal traction on the chordae tendineae to the mitral valve. Therefore, during systole, when the septum bulges further posteriorly into the outflow tract, the anterior mitral valve leaflet is held in the outflow tract forming the posterior aspect of a dynamic obstruction. Direct observation at the time of surgery to relieve the obstruction has confirmed the role of the asym-

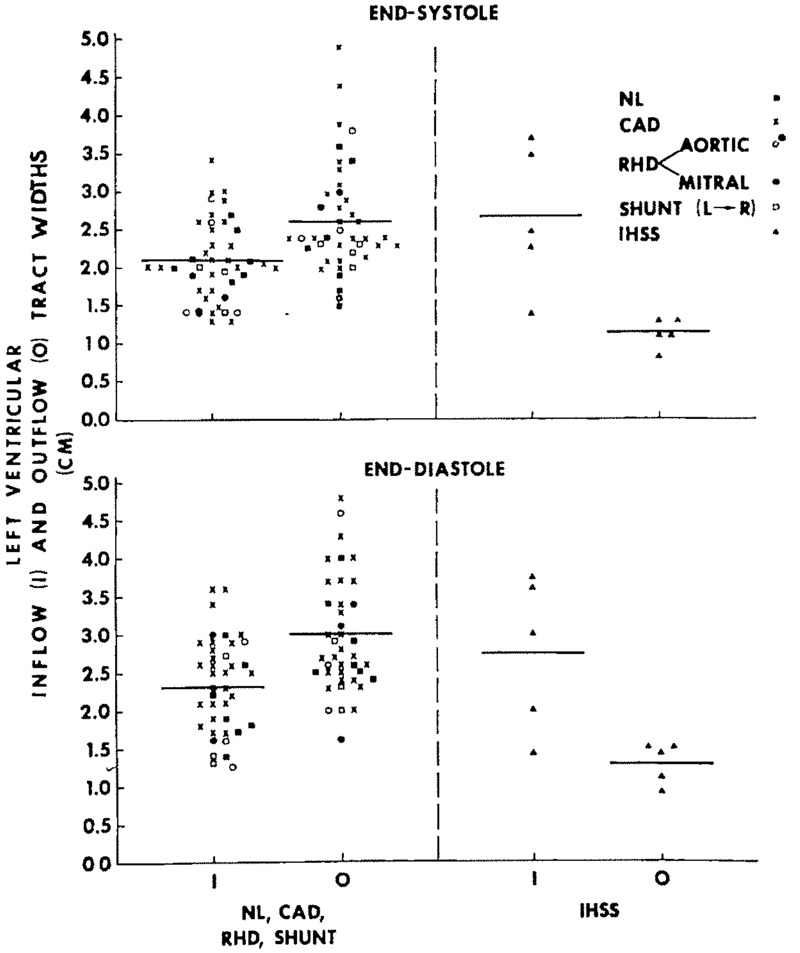

FIG. 3 *Graph depicting the individual and mean inflow (I) and outflow (O) tract widths in patients with idiopathic hypertrophic subaortic stenosis (IHSS) and in all other patient groups. The difference between the mean O widths for IHSS and the other patients is highly significant ($P < 0{\cdot}001$). The I widths are not statistically different. Abbrevations: NL=normal; CAD=coronary artery disease; RHD=rheumatic heart disease; Shunt (L→ R)=left-to-right shunt.*

metrical septal hypertrophy in the anterior displacement of the anterior mitral leaflet causing ballooning of the valve into the outflow tract and systolic obstruction (Bjork, 1964). As shown in the present study, the position of the mitral valve is abnormal during the entire cardiac cycle, and appreciable outflow tract narrowing exists even at the beginning of systole. During systole motion of the septum and mitral valve results in slight further narrowing of the outflow tract.

Echocardiography has confirmed the participation of the anterior mitral leaflet in the systolic narrowing of the left ventricular outflow tract in idiopathic hypertrophic subaortic stenosis (Gramiak *et al.*, 1969; Moreyra *et al.*, 1969; Popp and Harrison, 1969; Shah *et al.*, 1969; Gramiak and Shah, 1971; Shah *et al.*, 1971; Abbasi *et al.*, 1972; Feigenbaum, 1972; Pridie *et al.*, 1972; Shah *et al.*, 1972; Henry *et al.*, 1973b; King *et al.*, 1973a; Williams *et al.*, 1973; Epstein *et al.*, 1974; Henry *et al.*, 1975), and three studies have successfully correlated the systolic anterior movement of the anterior mitral leaflet with the pressure gradient from left ventricle to aorta (Popp and Harrison, 1969; Shah *et al.*, 1971; Henry *et al.*, 1973b). However, few (Gramiak and Shah, 1971; Epstein

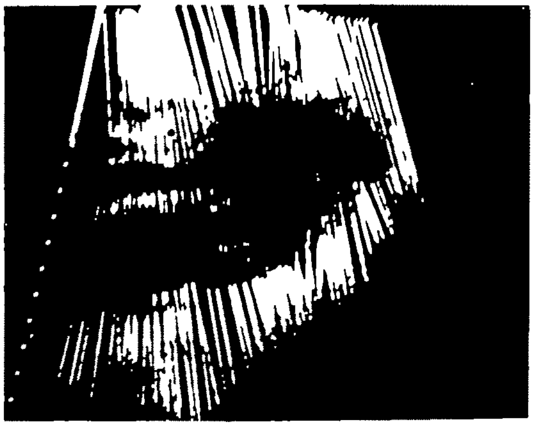

FIG. 4 *End-diastolic B-scan from a patient with idiopathic hypertrophic subaortic stenosis. The outflow tract continues to be narrowed despite left ventricular relaxation. The outflow tract width is 0·9 cm, and the ratio of outflow to inflow tracts is 0·32. The distance between the interval markers represents 1 cm.*

et al., 1974; Henry *et al.*, 1975) have commented on the degree of narrowing of the outflow tract, though many of the published echocardiograms show striking anterior displacement of the entire mitral valve echo in the left ventricular cavity. Using B-scan ultrasonography it is simple to measure accurately the width of the outflow tract. This study has shown that the average width of the outflow tract at end-systole in idiopathic hypertrophic subaortic stenosis in the plane of the scan is 1·1 cm, in contrast to the significantly wider outlet of 2·6 cm in all other patients studied (P < 0·001) or 2·4 cm in the normal group (P < 0·01). Persistence of the narrow outflow tract at end-diastole is well shown in Fig. 4 from a patient with typical echocardiographic and phonocardiographic features of idiopathic hypertrophic subaortic stenosis who did not undergo cardiac catheterization. Significant differences exist between the average end-diastolic width of 1·3 cm in these patients and 3·0 cm in all other subjects or 2·9 cm in patients with normal hearts (P < 0·001). These measurements are similar to those of Henry *et al.* (1975) made with a real-time two-dimensional sector scanner. Echocardiographic measurements of the outflow tract width in idiopathic hypertrophic subaortic stenosis are similar to those made by standard angiographic techniques (Fix *et al.*, 1964). In addition, as noted in Fig. 2 and 4, the outflow tract is not narrowed at a single point, but over a distance of several centimetres, the entire length of the visualized anterior leaflet of the mitral valve.

The outflow tract narrowing probably results from a combination of anterior displacement of the anterior mitral leaflet and inward bulging of the interventricular septum. The relative importance of each factor cannot be established from this study. The average normal left ventricular inflow tract width of 2·1 cm is considerably less than that found in ventricles of patients with idiopathic hypertrophic subaortic stenosis (2·7 cm). Though one patient (Case 2) with a very narrow I prevents this difference from becoming statistically significant, the observation suggests that anterior displacement of the mitral valve is indeed plausible and may account for the wider I and narrower O in patients with idiopathic hypertrophic subaortic stenosis.

TABLE 2 *Echocardiographic measurement of left ventricular inflow and outflow tracts*

Condition	*No. of patients*	*End-systole* O (cm)	*End-systole* I (cm)	*End-systole* O/I	*End-diastole* O (cm)	*End-diastole* I (cm)	*End-diastole* O/I
Normal	7	2·4±0·3*	2·1±0·1	1·1±0·1	2·9±0·2	2·1±0·2	1·5±0·1
IHSS	5	1·1±0·1§	2·7±0·4†	0·5±0·1§	1·3±0·1¶	2·7±0·5†	0·6±0·1¶
Other cardiac disorders							
CAD	26	2·7±0·1†	2·1±0·1†	1·4±0·3†	3·1±0·1†	2·5±0·1†	1·5±0·4†
L→R shunt	4	2·3±0·0†	2·0±0·5†	1·4±0·1†	2·6±0·3†	2·0±0·6†	1·3±0·1†
Valvular disease							
Aortic	3	2·9±0·5†	1·8±0·4†	1·8±0·5†	3·1±0·8†	2·0±0·5†	1·7±0·6†
Mitral	3	2·5±0·4†	1·6±0·1‡	1·5±0·2†	2·7±0·6†	2·3±0·4†	1·2±0·1†

*Mean ± standard error of the mean.

Significance of difference between measurements in normal and pathological conditions:

†P > 0·1
‡P < 0·05
§P < 0·01
¶P < 0·001.

Abbreviations: O = width of left ventricular outflow tract; I = width of left ventricular inflow tract; IHSS = idiopathic hypertrophic subaortic stenosis; CAD = coronary artery disease; L→R shunt = left-to-right shunt.

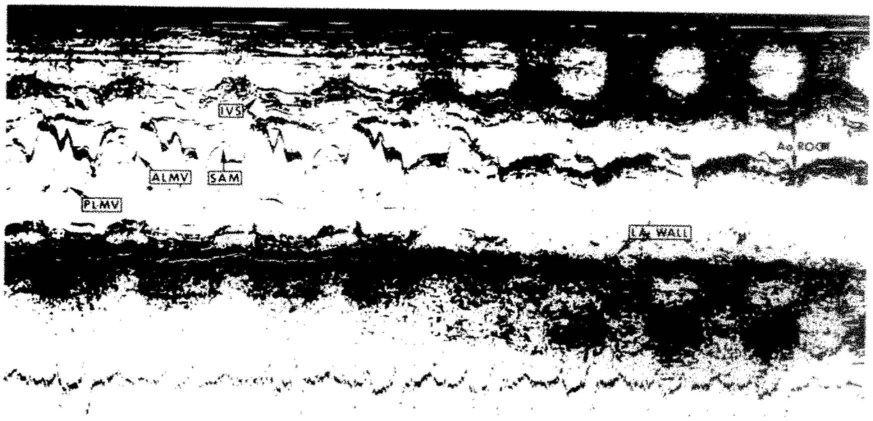

FIG. 5 *A strip chart recording of an echocardiographic cardiac sweep in a patient with idiopathic hypertrophic subaortic stenosis. Note the anterior position of the mitral valve echo. As the transducer was moved in a cephalad direction (left to right on the strip chart recording), the aortic (Ao) root echoes became apparent. That the mitral valve is indeed anterior is conclusively shown by comparing the relative positions of the anterior leaflet of the mitral valve (ALMV) and the Ao root. In this recording one also notes a much thickened interventricular septum (IVS) and a prominent systolic anterior movement (SAM) of the mitral valve echo. Interestingly, as the transducer was moved in a cephalad direction, the size of the SAM diminished, until it almost disappeared in the last recorded mitral valve echo in the strip. Abbreviations: LA=left atrial; PLMV=posterior mitral valve leaflet.*

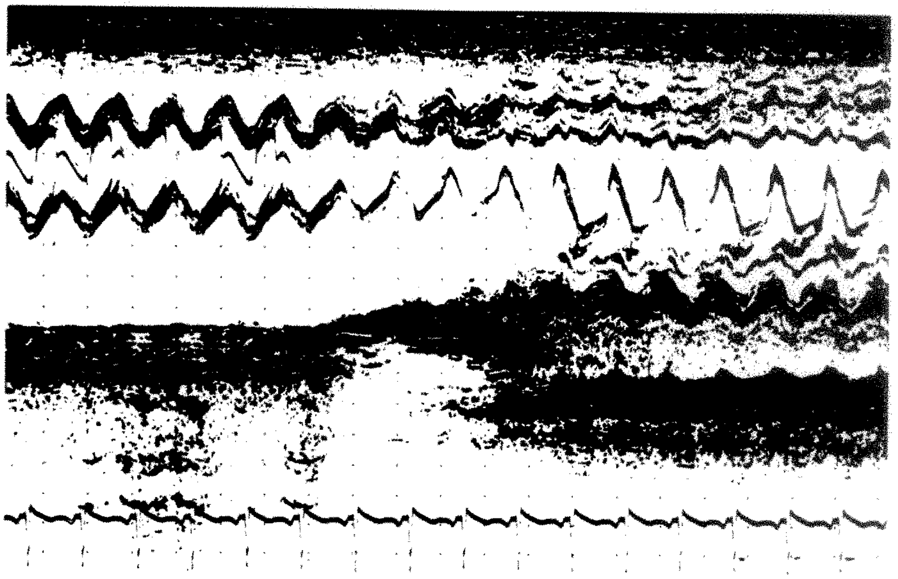

FIG. 6 *An ultrasonic cardiac sweep from a patient with a normal heart. The mitral valve is in a normal position relative to the aortic root and the left ventricular cavity. This position of the leaflet should be compared to the abnormal position of the mitral valve in a patient with idiopathic hypertrophic subaortic stenosis (Fig. 5).*

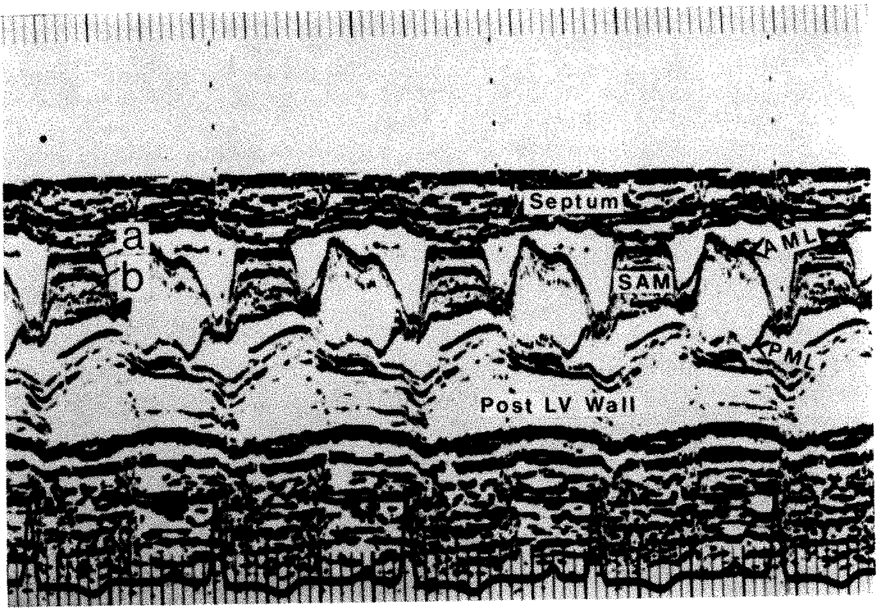

FIG. 7 *A strip chart recording of an echocardiogram in a patient with idiopathic hypertrophic subaortic stenosis.* The anterior position of the mitral valve echo is again noted. The systolic anterior movement (SAM) ('a') is also readily apparent. However, during systole there are multiple linear echoes ('b') immediately behind echo 'a'. It appears that different portions of the anterior mitral leaflet (AML) are drawn varying distances into the outflow tract, possibly because of a Venturi effect. Thus the SAM may represent the motion of only a small part of the mitral valve leaflet, perhaps the free edge or redundant valve tissue, while the major portion of the leaflet may move relatively little.*
Abbreviations: PML=posterior mitral leaflet; post LV wall=posterior left ventricular wall.
**Recorded with Hoffrel Series 101 Ultrasonoscope interfaced with a Cambridge Multichannel recorder and strip chart recorder.*

The above observation is probably not a result of the intrinsically small ventricle of these patients. Subjects with mitral stenosis and equally small left ventricular volumes had normal outflow tract dimensions and spatial orientation of the mitral valve. Therefore, the size of the outlet was not directly dependent on the size of the heart. We have studied only 3 patients with aortic valve disease and 2 patients with significant mitral stenosis, though King (1973) has published a B-scan from one further patient with mitral stenosis. In all these 6 patients the outflow tract measurement and the O/I ratio are in the expected normal range.

The narrowed outflow tract and the anterior position of the mitral valve can be detected as readily by careful time motion techniques as by B-scanning. The standard echocardiographic cardiac sweep (Fig. 5) shows this anterior position and confirms the close approximation of the mitral valve to the thickened septum. Comparison with a cardiac sweep of a normal mitral valve (Fig. 6) emphasizes the abnormal mitral valve position in the left ventricle of a patient with idiopathic hypertrophic subaortic stenosis. Detection of an abnormally anterior position of the mitral valve can be helpful when other echocardiographic signs of idiopathic hypertrophic subaortic stenosis are equivocal.

The present B-scan study suggests that the left ventricular outflow tract is significantly narrowed throughout the cardiac cycle with only small increases in width during diastole. Examination of a standard mitral valve echogram from a patient with idiopathic hypertrophic subaortic stenosis (Fig. 7) confirms the minimal difference in end-systolic and end-diastolic positions of the anterior leaflet. The marked outflow tract narrowing during mid-systole was not recorded with B-scanning techniques in the 2 patients studied at this time in the cardiac cycle. In contrast, real time sector scans have shown systolic anterior movement of the tip of the anterior leaflet (Henry *et al.*, 1975). The B-scan can measure the outflow tract in only 1 plane. It is possible that a scan in a perpendicular plane might have shown more significant outflow tract narrowing during systole. B-scanning records reflection of ultrasound from the main body of the anterior mitral leaflet, and perhaps may not record the motion of that part of the leaflet showing systolic anterior movement on standard echocardiograms; better resolution may make this apparent in B-scans.

Recent observations (King *et al.*, 1974; Rossen *et al.*, 1974) have questioned the central importance of the systolic anterior movement in the generation of the obstruction. In several patients simultaneous recording of the echocardiogram and left ventricular and aortic pressures has shown no gradient at a time when an obvious systolic anterior movement was present (King *et al.*, 1974; Rossen *et al.*, 1974). Furthermore, the systolic anterior movement may disappear before end-systole at a time when haemodynamic evidence of obstruction persists (Pierce *et al.*, 1964). In only one study has it been shown to persist to end-systole (Pridie *et al.*, 1972). Angiography has usually shown the systolic movement of the mitral valve leaflets anteriorly into the left ventricular outflow tract and the maintenance of this position until the onset of diastole (Simon *et al.*, 1967; Adelman *et al.*, 1969; Simon, 1972), though one study reported radiolucent structures appearing only transiently in the outflow tract in mid-systole in some patients (Simon *et al.*, 1967). Thus, the precise cause of the outflow tract obstruction is not apparent. It is possible that the anterior anatomical position of the mitral leaflet now shown by both B-scans and real time sector scans (Henry *et al.*, 1975) contributes to the critical narrowing of the outflow tract and is in part responsible for the pressure gradient. However, this would not explain the dynamic nature of the obstruction. Multiple systolic echoes as seen in Fig. 7 may indicate that different portions of the leaflet are drawn varying distances into the outflow tract, perhaps resulting from a Venturi effect (Wigle, Adelman, and Silver, 1971). Perhaps obstruction is determined by simultaneous narrowing of the outflow tract at several points.

B-scan ultrasonography has enabled us to examine the complex geometrical and anatomical relations in idiopathic hypertrophic subaortic stenosis and thus gain further insight into the pathophysiology of this disorder. The main body of the anterior mitral leaflet appears to be displaced anteriorly; this observation has made possible the definition of additional diagnostic criteria applicable to standard time motion echocardiography. The anterior position probably contributes to the outflow tract obstruction. The precise relation of the abnormal leaflet *position* to the previously defined systolic anterior movement and the relative haemodynamic significance of each remain to be determined.

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Immunological studies in congestive cardiomyopathy in Cameroon

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Significantly higher levels of immunoconglutinin were found in the sera of 40 Cameroonian patients aged between 15 and 80 years with congestive cardiomyopathy than in a matched group of normal Cameroonian controls. C3 values were also abnormal in the group with congestive cardiomyopathy, and a negative correlation was found between the C3 and immunoconglutinin values, indicating complement incorporation into immune complexes. Further, the levels of immunoglobulins G, M, and A were all raised, the most striking increase being of IgM, which was greater than in the normal controls and in a group with 'other cardiac disease' studied for comparison. Complement-fixing autoantibodies to cardiac muscle of the class IgG and IgM were found by immunofluorescence techniques in a significant proportion of the patients with congestive cardiomyopathy. Finally, evidence of trypanosomiasis was found by immunofluorescence tests in 27·5 per cent of patients with congestive cardiomyopathy, compared with 8·5 per cent of patients with other cardiac disease, and 1·9 per cent of normal Cameroonian controls selected randomly.

We think that some cases of congestive cardiomyopathy in Cameroon may be caused by untreated subclinical attacks of African trypanosomiasis which produce immune complexes that damage the cardiac tissue where the parasite is lodged. Secondary autoimmune carditis modifies the course of the disease, with the resulting end-stage picture.

Congestive cardiomyopathy has been defined as a disorder of heart muscle of unknown aetiology or association which is characterized by poor systolic function (Oakley, 1972). It has been variously known as idiopathic cardiomegaly (Reisinger and Blumenthal, 1941), nutritional heart disease (Gillanders, 1951), cryptogenic heart disease (*South African Medical Journal*, 1960), cardiovascular collagenosis (Becker, Chatgidakis, and Van Lingen, 1953), 'a cardiac disease of unknown aetiology' (Stuart and Hayes, 1963), and heart muscle disease (Eddington and Jackson, 1963).

Although mainly prevalent in the tropics, where it is an important cause of cardiac pathology, its incidence in temperate climates is probably underestimated (Hutt, 1972). Among the suggested causes are alcohol (Brigden and Robinson, 1964), the peripartum period (Walsh *et al.*, 1965), viral infections (Bengtsson, 1972; Grist and Bell, 1969), systemic hypertension (Kristinsson, 1969; Goodwin, 1970), and parasitic infections such as filaria and trypanosomiasis (Shaper *et al.*, 1968).

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Sanders (1963) and Sanders and Ritts (1965) suggest an immunological basis for the disease on the evidence of autoantibodies to cardiac tissue found in the sera of many patients with idiopathic cardiomegaly, by indirect immunofluorescence tests, and of intense staining deposits of gammaglobulin in the sarcolemma and subsarcolemmal regions of ventricular muscle found on cardiac biopsy or at necropsy. Dodson *et al.* (1967), using tanned red cell haemagglutination techniques, found antibodies to cardiac muscle in 2 out of 5 patients with cardiomyopathy. Furthermore, sustained high levels of antiheart antibodies in the serum, induced by repeated injection of heart antigens, resulted in carditis in animals (Kaplan and Craig, 1963). These animals also had autoantibodies to autologous heart shown by immunofluorescence, complement fixation, and flocculation techniques, and deposits of bound gammaglobulin were detected in the cardiac myofibres around the focal lesions.

On the other hand, Fletcher and Wenger (1968) found no difference in the incidence of antiheart antibodies (by immunofluorescence) in 34 patients with primary myocardial disease and in 71 control subjects. In Uganda van der Geld (1964), van der Geld *et al.* (1966), and Shaper *et al.* (1967) also found a high incidence of antiheart antibodies in both patients with idiopathic cardiomegaly and controls. Clearly, in view of these conflicting reports, further studies are needed to elucidate the role of immune mechanisms, if any, in the pathogenesis of congestive cardiomyopathy.

Patients

Patients were selected who conformed with the WHO criteria for 'cardiomegaly of unknown origin' (World Health Organization, 1967): cardiac enlargement associated with biventricular cardiac failure; pulse of usually small volume, sinus rhythm with occasional ectopic beats; diastolic pressure either normal, or if raised to 100 to 130 mmHg (13·3 to 17·3 kPa), falling to normal after treatment of the heart failure; apex beat forceful and often associated with a left parasternal heave; thrills and murmurs of mitral and tricuspid incompetence, characteristically diminishing or disappearing on treatment; and a third sound commonly present at the apex even after correction of overt failure.

Laboratory investigations were undertaken to exclude, when possible, liver, kidney, or thyroid disease; anaemia and sickle-cell disease; collagen vascular disorders; syphilis; acute rheumatic fever; and diabetes. Chest *x*-ray examination and 12-lead electrocardiograms were recorded routinely, but owing to lack of facilities cardiac catheter studies were not undertaken.

Of the 40 patients fulfilling these criteria 19 were men, mean age 47·5 years, and 21 were women, mean age 43·5 years. Nine (22·5%) of these had the sickle-cell trait (haemoglobin genotype AS), the same incidence as reported previously in the 'normal' population of Yaounde (Languillon, 1957; Gamet and Labes, 1964).

Materials and methods

The sera collected from several groups of subjects were separated within a few hours and stored in aliquots at -20°C to prevent thawing and refreezing. The groups comprised (*a*) 40 patients with congestive cardiomyopathy; (*b*) 52 randomly selected Cameroonian blood donors; and (*c*) 26 patients with non-hypertensive cardiac disease (designated 'other cardiac diseases'). The group of 26 comprised 13 patients with acute myopericarditis—2 of trypanosomal origin and the remaining 11 of viral aetiology (Coxsackie A and B, polio and Echo virus)—6 patients with rheumatic heart disease; 6 patients with hypertrophic obstructive cardiomyopathy; and 1 with endomyocardial fibrosis.

Sera from the above three groups of patients were studied for immunoglobulins, B_{1c}/B_{1a} globulins (C3), immunoconglutinins, and antitrypanosomal antibodies. Antibodies to cardiac, skeletal, and smooth muscle tissue were determined using the indirect immunofluorescence techniques in sera from (1) all the patients with congestive cardiomyopathy and other cardiac diseases; (2) 31 of the 52 Cameroonian blood donors; (3) 50 randomly selected Europeans who had never lived in Africa; and (4) 20 healthy Cameroonian medical students.

Immunoglobulins

IgA, IgG, and IgM were estimated by the single radial immunodiffusion method (Mancini, Carbonara, and Heremans, 1965) using the same batch of commercial antisera (Wellcome diagnostic reagents). All determinations were performed under identical conditions of temperature and the plates were read after 48 hours. Pooled Cameroon normal serum, previously related to WHO reference serum, was used as the working standard reference serum. Log transformation of the data was used for statistical analysis, the results being expressed as international units per millilitre (IU/ml). In the case of IgM, where many results were very high, high dilutions of the sera were used to obtain accurate readings.

B_{1c}/B_{1a} (C3) globulins

These were similarily determined by the single gel diffusion precipitation technique (Mancini *et al.*, 1965), and the values expressed as a percentage of the WHO reference serum.

Immunoconglutinin estimation

Immunoconglutinin was titrated by the method 2A of Coombs, Coombs, and Ingram (1961) incorporating the 'sedimentation pattern' technique of Lachmann (1966). The anti-Forssman serum used was raised by successive courses of immunization with Forssman hapten and fractionated to obtain a macroglobulin through Sephadex G-200. The sedimentation patterns in these plates (using 0·6% alexinated sheep red cells) were assessed, after allowing the reaction to proceed overnight at 4°C, by the technique of 'pouring'. The following controls were included in each run:

(*a*) *Positive control*—pooled serum from patients with trypanosomiasis.

(*b*) *Negative control*—serum known to have no demonstrable immunoconglutinin activity.

(*c*) *Specificity control*—sheep red cells were exposed to heat inactivated (56°C for 30 min) horse serum and anti-Forssman serum. The immunoconglutination reaction was performed with these cells and the test serum, at the highest concentration used in the titration, to control for positive sedimentation other than conglutination.

Immunofluorescence

Immunofluorescence tests were performed using the sandwich technique to detect autoantibodies to heart and other muscle tissues. Tests were performed on the following tissues: (*a*) human fetal heart; (*b*) rat heart; (*c*) rat kidney, for smooth muscle in blood vessel wall; and (*d*) rat skeletal muscle. All examinations were under-

TABLE 1 *Mean (±SD) levels of immunoglobulin (IU/ml) and C3 (% of WHO ref. serum) in controls, patients with congestive cardiomyopathy, and patients with other cardiac diseases together with ratios of variance of patients from controls.*

	Controls (n=52)	*Congestive myopathy (n=40)*		*Other cardiac disease (n=26)*	
		Level	*Variance ratio*	*Level*	*Variance ratio*
IgG	170·2±57·4	192·2±96·3	2·28 (F<0 005)	173±87·2	1·94 (F<0·05)
IgA	120±29·2	149±53·6	2·95 (F<0·005)	121±47·7	2·52 (F<0·01)
IgM	182±64	339±215	5 37 (F<0·005)	228±67	0·55 (NS)
C3	120±23·3	125±53 5	11·25 (F<0·005)	156±42·8	7·47 (F<0·005)

taken on 6μ cryostat sections mounted on slides and air-dried overnight.

Sera were tested diluted 1/10, 1/20, and 1/40. The conjugate (Wellcome diagnostic reagents, Rabbit anti-human IgA; IgG; IgM—FITC) was diluted 1/50. The sera were applied for 20 minutes, followed by washing in phosphate-buffered saline (PBS), *p*H 8·0, for 30 minutes. The conjugate was then added and after 20 minutes this was rinsed off three times in phosphate-buffered saline before the slide was finally washed for 2 hours. The class of antibody was identified by purified anti-human IgG-FITC, IgM-FITC, IgA-FITC. Complement-fixing ability was investigated with anti-B_{1c}/B_{1a} globulin fluorescein conjugate preparation, after the addition of either fresh or heat-inactivated (56°C for 30 min) serum from normal European controls.

All sera were coded, a known positive and negative control included in each run, and all read by the same observer with a Nachet 200 microscope with a quartz iodide light source. The results were recorded as positive or negative at the dilution of serum employed, and the site of staining recorded as sarcolemmal/subsarcolemmal or microsomal.

Trypanosomiasis

The indirect fluorescence antibody technique has been shown to be the most sensitive method of detecting trypanosomal infection (Alvarez, Cerisola, and Rowedder, 1967). *T. gambiense* is antigenically similar to *T. rhodesiense*, and the latter was used as antigen in testing for antibodies to *T. gambiense* in the test sera. The indirect fluorescence was performed by the sandwich technique and serial dilutions of the test sera were used to obtain the titre of antibodies present.

Results

Immunoglobulins

The mean levels of IgG and IgM in the control group of Cameroonians were significantly higher than in appropriately matched Caucasians, a finding that has been previously reported by Turner and Voller (1966) and Rowe *et al.* (1968). The mean values of IgM, IgG, and IgA in the patients with congestive cardiomyopathy were all significantly higher than those of the Cameroonian controls (F<0·005, variance ratio test) (Table 1). In addition IgM values greater than 2 SD above the mean were found in 18 patients with congestive cardiomyopathy, and in 12 of these the values exceeded 400 IU/ml (Fig. 1). In the cases of other cardiac disease the IgG levels were significantly different by the variance ratio test from the controls (F<0·05) and the IgA (F<0·01). In the case of IgM, though the variance ratio test showed no significant difference from the controls analysis of the means showed a difference at the 95 per cent confidence limit.

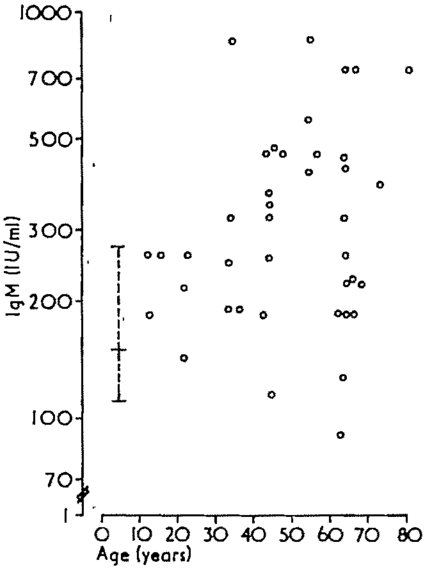

FIG. 1 *Serum IgM levels (IU/ml) in patients with congestive cardiomyopathy. Vertical interrupted line indicates geometric mean plus 2 SD above and 1 SD below mean of data from normal Cameroonian controls.*

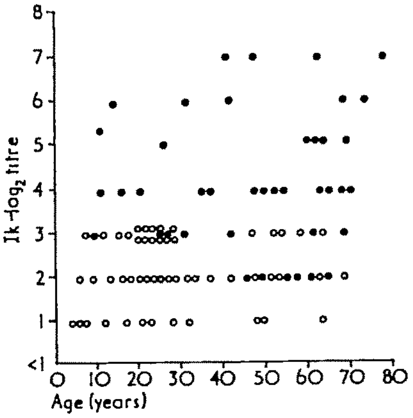

FIG. 2 *Serum immunoconglutinin (IK) titres in patients with congestive cardiomyopathy (●) and in matched Cameroonian controls (○).*

Immunoconglutinin and B_{1c}/B_{1a} (C3) globulin

Immunoconglutinins are autoantibodies of the immunoglobulin classes G, M, or A which react with the complement components C3 (Lachmann and Coombs, 1965) and C4 (Lachmann, 1966) after their binding to antigen-antibody complexes (Coombs *et al.*, 1961). The values obtained in the group of patients with congestive cardiomyopathy and in the normal Cameroonian controls is shown in Fig. 2. The difference is highly significant ($P<0.005$ Student's *t* test). In the patients with other cardiac diseases the mean immunoconglutinin titres of those with myopericarditis (4·1) and rheumatic fever (4·7) were not significantly different from those with congestive cardiomyopathy, whereas patients with hypertrophic obstructive cardiomyopathy and endomyocardial fibrosis had mean values of 1·4 and 2, respectively, similar to the normal Cameroonian controls. Interestingly, the highest immunoconglutinin values (range 5 to 8 $-\log_2$ titre) obtained in this group of patients with other cardiac diseases were found in the sera from 4 subjects with trypanosomal infection. Two of these had trypanosomal myopericarditis and the other two were from the group of 6 patients with clinical rheumatic heart disease. Trypanosomiasis is a well-known cause of high serum immunoconglutinin levels (Coombs *et al.*, 1961; Ingram *et al.*, 1959).

The mean (±SD) C3 values in the control sera were 120 IU/ml±23·3. The mean values in the group with congestive cardiomyopathy showed a wider scatter 125 IU/ml±53·5. However, there was a highly significant difference between the two groups ($F<0.005$ variance ratio test). The mean of the patients with other cardiac diseases was 156 IU±42·8, which again was a highly significant difference ($F<0.005$ variance ratio test). Interestingly, the lowest C3 levels tended to be associated with the highest immunoconglutinin levels (Fig. 3), the coefficient of correlation being −0·639.

Immunofluorescence

There was a high level of antibodies to the tissues tested in both the patients with congestive cardiomyopathy and those with other cardiac disease, with no significant difference between the two groups of patients. Only a few in the control group comprising sera from randomly selected Cameroonian blood donors had antibodies to cardiac muscle, whereas antibodies to skeletal muscle were found in many (Table 2). No antibodies to skeletal or cardiac muscle were found, however, in the control sera from healthy Cameroonian medical students and Europeans who had never lived in Africa.

One notable finding was of the sarcolemmal/subsarcolemmal staining in the skeletal muscle, whereas in the fetal heart sections the staining was microsomal. The antibodies were of the immunoglobulin class G and M, and were complement binding.

Trypanosomiasis

Although *T. gambiense* is antigenically close to *T. rhodesiense* the results tended to underestimate the levels of antibodies in the samples. Nevertheless, of the 40 patients with congestive cardiomyopathy 11 (27½%) showed evidence of trypanosomal in-

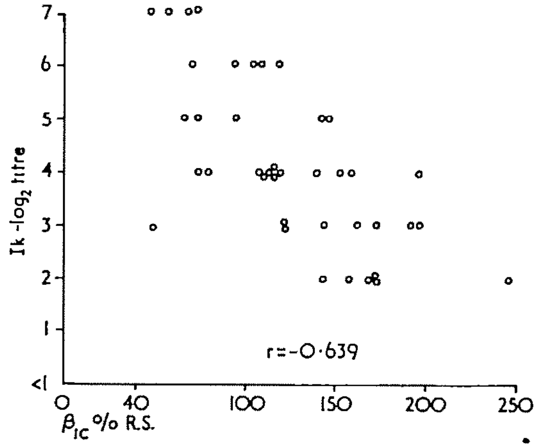

FIG. 3 *Serum immunoconglutinin (IK) titres of patients with congestive cardiomyopathy plotted against corresponding B_{1c}/B_{1a} (C3) values.*

TABLE 2 *Percentage of patients and controls showing immunofluorescent tissue antibodies at various serum dilutions.*

Diagnosis	*No. studied*	*Skeletal muscle*			*Heart*			*Smooth muscle*		
					Serum dilutions					
		1/10	*1/20*	*1/40*	*1/10*	*1/20*	*1/40*	*1/10*	*1/20*	*1/40*
Congestive cardiomyopathy	40	75	60	28	60	35	28	40	25	20
Other cardiac diseases	26	85	72	31	65	55	40	30	27	22
Cameroonian blood donors	31	40	35	9	5	3	—	Not done		
Cameroonian medical students	20	—	—	—	—	—	—	—	—	—
Europeans	50	—	—	—	—	—	—	—	—	—

fection, 3 with a titre of 1/16, and 9 with a titre of 1/64. Two patients with myopericarditis also had antibodies at a titre of 1/64, and as the trypanosomal antibodies were also found in the pericardial fluid they were diagnosed as having trypanosomal heart disease. Two further patients with acute myopericarditis, clinically diagnosed as acute rheumatic fever, were also found to have antibodies to *T. rhodesiense* (both at a titre of 1/64), suggesting a plurality of pathology or that they were masquerading as rheumatic heart disease. Only one (1·9%) among the sera from 52 randomly selected Cameroonian blood donors was found to have antibodies to trypanosomiasis at a titre of 1/16.

Discussion

Congestive cardiomyopathy is probably the end-stage of many different cardiac insults that act through the same mechanism to produce the cardiac damage. Our results suggest that the pathogenesis may be immunological.

Immunoconglutinin concentrations are abnormally high in conditions with immunological disturbance such as systemic lupus erythematosus and progressive nephritis (Coombs *et al.*, 1961; Ingram, 1959; Ngu and Soothill, 1969). Immunoconglutinins are autoantibodies that react with some complement components after their binding to antigen-antibody complexes, and recently it has been shown that they enhance the clearance of soluble immune complexes (Ngu and Lambert, 1976). Thus, the significantly raised immunoconglutinin titres in the sera of our patients with congestive cardiomyopathy compared with normal Cameroonian controls suggest that similar mechanisms were at work. This view is further substantiated by the negative correlation between the immunoconglutinin levels and C3 levels in the group with congestive cardiomyopathy, indicating complement incorporation in immune complexes. Nevertheless, the raised immunoconglutinin titres and congestive cardiomyopathy could possibly be unrelated and independently related to the agent or agents that precipitated the cardiac damage. The raised immunoconglutinin levels in the patients with acute rheumatic fever and trypanosomal myopericarditis are in keeping with the known immunopathogenesis of these diseases. The moderate rise in those with viral myopericarditis is consistent with the findings in other viral infections (Coombs *et al.*, 1961), though the precise mechanism operating in such cases is still unclear.

Immunoglobulins are produced in response to a variety of stimuli. The higher levels of immunoglobulins in the patients with congestive cardiomyopathy and other cardiac diseases compared with controls might in part be due to autoantibodies to cardiac tissue. However, the striking increase in IgM levels was seen only in patients with congestive cardiomyopathy and consequently must derive from a different stimulus. Persistent parasitization is known to be associated with increased IgM synthesis (Lambert and Houba, 1974), and possibly a difference of specific parasitic infection among the groups tested rather than any difference in host response to the infection is responsible for this.

Antibodies to cardiac tissue have been reported in a variety of heart diseases, but except in rheumatic fever, in which they may play a pathogenic role (Goldstein, Halpern, and Robert, 1967), their significance is far from clear (Kaplan and Frengley, 1969). The production of carditis in animals after a prolonged circulation of antibodies to cardiac tissue suggests a causal role (Kaplan and Craig, 1963). Though this might also be the case in congestive cardiomyopathy, the alternative view that these antibodies are produced in response to cardiac damage by other agents cannot be refuted (Gery, Davies, and Ehrenfield 1960). We found cardiac antibodies of the G and M classes. That they participate in the formation of immune complexes was suggested by their complement-fixing ability and the abnormal C3 and immunoconglutinin values in the sera with the highest IgM and IgG levels. The high incidence of autoantibodies in the patients with other cardiac diseases is to be expected since they are known to occur in rheumatic fever and pericarditis (Kaplan and Frengley, 1969), which indeed accounted for all but one of the positive cases in that group of patients. Our results are at variance with those of Shaper *et al.* (1967), van der Geld (1964), and van der Geld *et al.* (1966) in that cardiac autoantibodies were found in the sera of only a minority of blood donors (Table 2). Their absence in the sera of healthy Cameroonian medical students suggests that they are indeed indicative of cardiac damage and that their presence in a few of the blood donors may have reflected undiagnosed disease. The high incidence of antibodies to skeletal muscle in the blood donors is difficult to explain.

Aetiology

Although *T. cruzi* is a well-known cause of heart disease in South America, in Africa, until recently, more attention has been paid to the effects of trypanosomiasis on the central nervous system. African trypanosomiasis certainly causes a panmyocarditis (Armengaud and Biram, 1960; Francis, 1972), including in some cases a valvulitis (Poltera, Cox, and Owor, 1975), with raised IgM and IgA levels (Armengaud and Biram, 1960). Lambert and Houba (1974) have found evidence for an immunopathogenic basis of the lesions in mice caused by *T. brucei*, as shown by the alterations of the complement components, granular deposits of immunoglobulins detected along the heart fibres by immunofluorescence, and a disseminated vasculitis with a preponderance of lesions in the heart and brain. These authors think that a similar mechanism operates in African trypanosomiasis.

T. gambiense is endemic in at least four areas of Cameroon, so that its incidence in the population varies with the geographic origin of the people concerned. Though the area in which this study was undertaken is not one where trypanosomiasis is endemic it is within easy reach of two such areas. Our findings of antibodies to *T. rhodesiense* in 27·5 per cent of patients with congestive cardiomyopathy in contrast to 8·5 per cent of patients with other cardiac diseases—excluding the two patients with trypanosomal myopericarditis—and 1·9 per cent of randomly selected blood donors suggests a causal relation. Indeed, trypanosomiasis is one of the most potent stimulators of immunoconglutinins (Coombs *et al.*, 1961; Ingram *et al.*, 1959) and IgM. That high levels of these antibodies were found in our patients with congestive cardiomyopathy, a significant proportion of whom had evidence of trypanosomal infection, is therefore not surprising. Furthermore, Cossio *et al.* (1974) found in cases of Chagas's disease a circulating immunoglobulin which reacted on indirect immunofluorescence with the endocardium, skeletal muscle, and vascular structures of other organs—findings similar to those in our patients with congestive cardiomyopathy.

We conclude that in untreated subclinical attacks of African trypanosomiasis immune complexes are produced which damage the cardiac tissue in which the parasite is lodged. Secondary autoimmune carditis may modify the course of the disease, with a resulting end-stage picture of congestive cardiomyopathy.

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Effects of intravenous nitroglycerin on left ventricular function and ST segment changes in acute myocardial infarction[1]

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It has been shown previously that 30-minute infusions of intravenous nitroglycerin in patients with acute myocardial infarction are able to lower left ventricular filling pressure and improve left ventricular function while lowering mean arterial pressure by only 7 mmHg (0·9 kPa). A decrease in ΣST in praecordial ST segment mapping studies during nitroglycerin infusion in patients with anterior infarction suggested a decrease in the extent of myocardial ischaemia. In the present study, 30 patients with acute myocardial infarction received 1- to 3-hour infusions of intravenous nitroglycerin at infusion rates sufficient to lower mean arterial pressure by an average of 22 mmHg (2·9 kPa). An improvement in ventricular function was noted in that subgroup of patients with the most severe left ventricular dysfunction. All patients with anterior myocardial infarction underwent serial ST segment mapping and, irrespective of the presence or absence of left ventricular failure, showed a decrease in ΣST during nitroglycerin infusion ($P<0·005$). These findings suggest that infusion of nitroglycerin improves left ventricular function and/or alters left ventricular compliance in patients with left ventricular failure complicating myocardial infarction and furthermore decreases ΣST in all patients, irrespective of the presence or absence of left ventricular failure, suggesting that the extent of myocardial ischaemia is decreased.

Vasodilator therapy with infusions of nitroprusside (Franciosa *et al.*, 1972; Chatterjee *et al.*, 1973), phentolamine (Kelly *et al.*, 1973; Gould *et al.*, 1974), or trimetaphan (Shell and Sobel, 1974) has been shown in patients with myocardial impairment to improve left ventricular function by reduction of afterload. A decrease in arterial pressure and thus in coronary perfusion might however result in an increase in the extent of myocardial ischaemia. It is uncertain whether the beneficial effect of afterload reduction in decreasing oxygen demand outweighs the potentially harmful effect of decreasing perfusion pressure and oxygen supply.

Sublingual nitroglycerin has been shown to improve ventricular function transiently in patients with myocardial infarction (Gold, Leinbach, and Sanders, 1972; Delgado *et al.*, 1975). However, a precipitous fall in arterial pressure can occur when the drug is administered by the sublingual route, and a resulting reflex tachycardia could increase infarct size (Delgado *et al.*, 1975). We have recently shown that intravenous nitroglycerin can be administered safely to patients with acute myocardial infarction (Flaherty *et al.*, 1975). Left ventricular filling pressure was lowered from an average of 22 mmHg to 12 mmHg (2·9 to 1·6 kPa), with an average of 7 mmHg (0·9 kPa) reduction in mean arterial pressure and without an associated increase in pulse rate. Serial praecordial ST segment mapping studies in those patients with anterior infarction suggested a decrease in the extent of the

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TABLE 1 *Nitroglycerin treated patients*

Case No.	*Age*	*Sex*	*Location and type of infarct*	*History of hypertension*	*History of previous infarct*	*Clinical class*	*Mortality*	*Onset of pain to study (hr)*	*Final TNG infusion rate (µg/min)*	*Duration of infusion (hr)*
1	58	M	I T	—	—	I	—	7·0	48	3
2	55	M	A T	+	—	II	—	6·0	17·6	1
3	38	M	A T	+	—	II	—	18·5	102·9	2
4	58	M	A T	—	—	I	—	3·5	13·6	1
5	60	M	I T	—	—	I	—	6·0	10	3
6	65	M	I T	—	—	I	—	4·0	36·5	3
7	71	F	A T	—	—	I	—	9·0	36·5	3
8	48	M	A T	+	—	I	—	5·0	102	1
9	55	M	I T	+	—	I	—	13·2	103	1
10	49	F	I T	—	—	I	—	21·3	199	1
11*	52	M	A T	+	+	II	+	5·0	72	1
12	55	M	A T	+	—	III	—	8·0	36·5	1
13	70	M	I T	—	—	II	—	6·0	50·5	3
14	59	M	I T	—	+	I	—	4·6	44·3	1
15	58	F	A T	+	+	II	—	6·0	166	2
16	62	M	I T	—	+	II	—	6·3	103	1
17	53	F	I T	+	—	I	—	18·3	17·6	1
18	56	F	I T	—	—	I	—	11·5	36·5	1
19	63	F	I T	+	—	II	—	5·0	73	1
20	42	M	A T	+	—	II	—	8·5	73	1
21	48	M	I T	+	+	II	—	6·5	100	1
22	61	F	A T	+	—	II	—	13·5	26·6	1
23	65	F	A T	—	—	II	—	7·0	57·5	1
24	46	M	A T	+	+	II	—	3·5	26·6	3
25	54	M	A T	+	—	II	—	6·0	10	2
26	63	M	I NTM	—	+	III	—	19 0	17·6	3
27	55	F	I T	+	—	II	—	6·0	26·6	1
28	62	M	I T	—	—	II	—	2·5	36·5	1
29†	58	M	A T	—	—	II	+	5·0	26·6	1
30	49	F	A T	—	—	II	—	6·0	51	1

*Case 11 died on day 17 of pulmonary embolus.

†Case 29 died on day 3 in cardiogenic shock with complete heart block.

A, anterior; I, inferior; T, transmural; NTM, non-transmural. Clinical class (Killip, 1968).

myocardial ischaemia during nitroglycerin infusion.

This study reports: (1) the infusion of intravenous nitroglycerin for longer durations and at higher infusion rates compared with those of the initial study, resulting in a mean decrease in mean arterial pressure of 22 mmHg (2·9 kPa) below control levels, and (2) the effects of this afterload reduction on left ventricular function and on the extent of myocardial ischaemia in 30 patients with acute myocardial infarction.

Patients studied

Control untreated patients

Seventeen patients with acute anterior transmural myocardial infarction underwent serial praecordial mapping studies for two hours during which nitroglycerin was not infused. Spontaneous changes in ST segments in these patients were compared with those changes recorded in patients receiving infusions of intravenous nitroglycerin. Of the 17 patients, 9 had Swan Ganz and arterial catheters in place during the serial mapping studies and subsequently received nitroglycerin after the two-hour control period. The remaining 8 control patients either refused nitroglycerin treatment, or entered the hospital at a time when intravenous nitroglycerin was unavailable or when another nitroglycerin study was in progress. Untreated patients were studied within 24 hours (mean 7·8±0·9 hours) of the onset of chest pain. Their mean age was 57·3 years. Four of these patients were in class I and 13 were in class II (Killip, 1968). These patients were given nasal oxygen, intravenous morphine for pain, and had electrocardiographic and cardiac enzyme evidence of acute myocardial infarction.

Nitroglycerin-treated patients

Thirty patients with acute myocardial infarction received intravenous infusions of nitroglycerin also within 24 hours (mean 8·3±0·9 hours) of the onset of chest pain (Table 1). Patients less than 75 years of age admitted to the coronary care unit with a high probability of an acute myocardial infarction by history and/or acute electrocardiographic abnormalities were candidates for the study. Patients meeting the above criteria were admitted to the study with informed consent, if intravenous nitroglycerin and the research team were available. The mean age of the nitroglycerin-treated patients was 56·3 years. There were 29 patients with transmural infarctions (15 anterior and 14 inferior) and one with a nontransmural inferior infarction. Ten of these patients were in Killip class I, 18 were in class II, and 2 were in class III. Excluded from this study were patients in cardiogenic shock and patients not in clinical shock, but with mean arterial pressures less than 75 mmHg (10·0 kPa). All patients were given nasal oxygen and intravenous morphine for pain. All patients had electrocardiographic and cardiac enzyme evidence of acute infarction and all were in sinus rhythm.

The 30 patients were retrospectively divided into 3 groups according to their initial left ventricular filling pressure and stroke work index. This division allowed evaluation of nitroglycerin therapy in patients with normal, mildly impaired, and moderately impaired left ventricular function.

Group I	10 patients with LVFP $\leq$12 mmHg (1·6 kPa).
Group II	10 patients with LVFP >12 mmHg (1·6 kPa) and SWI $\geqslant$40 g m per m^2.
Group III	10 patients with LVFP >12 mmHg (1·6 kPa) and SWI <40 g m per m^2.

Methods

Praecordial mapping studies in untreated patients

A 48-lead praecordial ST segment map consisting of 6 rows of 8 leads was obtained in all 17 control patients with anterior transmural myocardial infarctions using an electrocardiographic standardization of 1 mV=20 mm (Reid *et al.*, 1974). Serial 16-lead recordings were made at 30-minute intervals for 2 hours. The 16 leads selected were the 2 rows of 8 leads which initially showed the maximum ST segment changes. The chest was marked for exact repositioning of the leads and the sum of the ST segment elevations in the 16 leads was defined as ΣST. If a given praecordial map showed both ST elevations and depressions, only the ST segment elevations were summed (Maroko *et al.*, 1972). Each of the serial praecordial ST segment maps obtained in the untreated patients was coded with a random number by a technician other than the one who would be analysing the ST segment changes. The technician reading the maps, therefore, had no knowledge of the sequence in which the maps had been obtained.

Protocol for nitroglycerin infusion in treated patients

The protocol for infusion of intravenous nitroglycerin was as follows. Left ventricular filling pressure as reflected by mean pulmonary artery wedge pressure or the pulmonary artery diastolic pressure was measured with a No. 7 Swan Ganz thermodilution catheter (Model No. 93-118-7F) introduced by cutdown through an antecubital vein. Arterial pressure was measured with a short plastic catheter inserted percutaneously or by cutdown into the radial artery. Arterial and venous pressures were measured with Statham P23Db and P37b transducers, respectively, and recorded on a Brush Mark II-40 four-channel direct writing recorder. Cardiac output was determined by thermodilution technique[1] (Ganz and Swan, 1972). The injectate consisted of 10 to 15 ml 5 per cent dextrose at room temperature. Each cardiac output reported is the mean of at least two serial measurements with a maximum allowed variance between individual measurements of 10 per cent. The reproducibility of these cardiac output measurements was previously reported (Flaherty *et al.*, 1975).

Aqueous solutions of nitroglycerin (500 μg/30 ml) were prepared as previously described, refrigerated, protected from light, and used within 4 weeks of preparation (Flaherty *et al.*, 1975). Significant loss of biological activity has been noted with storage greater than 4 weeks.

The infusion of nitroglycerin was begun at 10 μg/min using a Harvard constant infusion pump. The rate of administration was increased stepwise at 3- to 5-minute intervals until the mean arterial pressure fell approximately 20 mmHg (2·7 kPa) below the control level. The study was designed so that the infusion was slowed or temporarily discontinued if arterial pressure fell to less than 50 mmHg (6·7 kPa) diastolic or if the heart rate rose by more than 20 beats/minute or fell to less than 50 beats/minute. A decrease in infusion rate was necessary only during the initial dose finding period in 12 of the 30 patients. The infusion rate was then maintained at the final level for a period of 1 to 3 hours. The average final infusion rate of nitroglycerin was 57·3 μg/min (range 10-199 μg/min). In 5 patients mean arterial pressure could not be lowered by more than 11 mmHg (1·5 kPa) despite increasing the infusion rate of nitroglycerin to 199 μg/min. However, mean arterial pressure did increase by 16 to 34 mmHg (2·1 to 4·5 kPa) after termination of the nitroglycerin infusion, suggesting that baseline arterial pressure was increasing during the infusion period in these 5 patients.

Haemodynamic values including arterial pressure,

[1] Edwards Cardiac Output Computer, Model 9500.

TABLE 2 *Changes in Σst in untreated patients*

Case No.	*ΣST (mm)* *Initial*	*60 min*	*120 min*
1	13	10	17·5
2	32·5	20·5	25·0
3	9·5	8	8·5
4	13·5	16	11
5	43·5	49·5	19·5
6	20	21	35·5
7	8·5	5·5	6·5
8	76	39	49·5
9	58	45·5	42·5
10	53	40	39·5
11	28·5	29	26
12	85·5	92·5	134·5
13	38	61	66
14	21	27	32
15	70·5	66	66
16	18	11·5	6
17	82·5	77·5	70
Mean	39·5	36·5	40·3
SE	6·5	6·3	7·8
P value		NS	NS

cardiac output, heart rate, and left ventricular filling pressure were measured on two occasions at least 10 minutes apart during the control period before starting the nitroglycerin infusion. These measurements were then repeated at 15-minute intervals throughout the infusion period. From these measurements derived values were obtained as follows:

Stroke work index (SWI):

$$\text{SWI (g m per m}^2\text{)} = \frac{\text{SVI} \times (\text{MSP} - \text{LVFP}) \times 1{\cdot}36}{100}$$

SVI = stroke volume index
MSP = mean systolic arterial pressure
LVFP = left ventricular filling pressure

Pressure-time per minute index (PTM):

$$\text{PTM (mmHg per min)} = \text{MSP} \times \text{ET} \times \text{HR}$$

HR = heart rate, ET = systolic ejection time, measured from the radial artery pressure record.

Peripheral resistance index (PRI):

$$\text{PRI (mmHg min/l per m}^2\text{)} = \text{MAP/CI}$$

MAP = mean arterial pressure, CI = cardiac index.

Serial praecordial ST segment mapping studies were performed on those 15 patients with anterior transmural myocardial infarctions, but not on those 15 patients with inferior infarction. After an initial 48-lead map, 16-lead recordings were made one hour before starting nitroglycerin infusion and then at 15 to 30-minute intervals simultaneously with each subsequent haemodynamic measurement. ΣST was computed as previously described for the control patients.

The same 'blind' reading procedure described for ST segment maps in the untreated group was employed for the praecordial ST maps obtained in the treated group. The technician reading the maps could not, therefore, differentiate maps obtained during the 2-hour control period from those obtained during nitroglycerin infusion. In 12 of the 15 patients the initial control ST segment map was obtained with all haemodynamic monitoring equipment and catheters in place. In the remaining 3 patients the lines were in the process of being placed at the time that the first control map was recorded.

Results

Praecordial mapping studies in untreated patients

The results of the two hours of control praecordial mapping studies in 17 patients with anterior transmural myocardial infarctions not receiving nitroglycerin therapy are presented in Table 2. There were no significant changes in ΣST noted during the 2-hour period of observation.

Haemodynamic and praecordial mapping studies in nitroglycerin treated patients

The haemodynamic effects of intravenous nitroglycerin in the total group of 30 patients are summarized in Fig. 1. The haemodynamic measurements and derived values for each of the 30 patients, divided into the three haemodynamic subgroups, are presented in Table 3. All data in Table 3 and in the text are expressed as the mean ± one standard error of the mean.

Mean arterial pressure was lowered from a mean of 108·3±3·9 mmHg (14·4±0·5 kPa) during the control period to a mean of 86·7±3·1 mmHg (11·5 ±0·4 kPa) at the time of maximal afterload lowering effect of nitroglycerin ($P < 0{\cdot}001$) (Fig. 1). The left ventricular filling pressure decreased from a mean of 16·7±1·4 mmHg (2·2±0·2 kPa) during the control period to 8·1±0·8 mmHg (1·1±0·1 kPa) at the time of maximal arterial pressure lowering ($P < 0{\cdot}001$). Heart rate in the total group of 30 patients did not change significantly during nitroglycerin infusion. In only 7 of the 30 patients did the heart rate increase during nitroglycerin. In those 7 patients heart rate increases of only 2 to 10 beats/minute were noted. Cardiac index decreased 8·8 per cent ($P < 0{\cdot}05$). There was no significant change in stroke work index when the total group of 30 patients was taken as a whole. Pressure-time per minute index fell 24·7 per cent ($P < 0{\cdot}001$), and peripheral resistance index fell 11·3 per cent ($P < 0{\cdot}001$).

TABLE 3 *Haemodynamic findings in 30 patients receiving intravenous nitroglycerin*

Case No.		*Heart rate (beats/minute)*		*Left ventricular filling pressure (mmHg)*		*Mean arterial pressure (mmHg)*		*Cardiac index (litres/min per m²)*		*Stroke volume index (ml per m²)*	
		C	*TNG*	*C*	*TNG*	*C*	*TNG*	*C*	*TNG*	*C*	*TN*
Group I											
1		78	65	11	2	102	86	2·60	2·36	33·3	36·6
2		75	85	11	6	140	120	1·72	1·66	22·7	19·7
3		110	112	7	2	124	104	2·40	2·00	21·8	17·9
4		85	64	10	2	106	78	1·84	1·58	21·6	24·7
5		87	94	6	3	178	122	2·79	2·58	32·1	27·5
6		68	63	9	3	91	66	1·54	1·48	22·7	23·5
7		106	108	12	5	116	106	2·10	1·45	19·8	13·4
8		68	74	10	7	98	74	2·92	2·00	42·9	27·0
9		79	71	11	3	102	80	2·64	2·30	33·4	32·4
10		95	92	9	6	94	74	2·64	2·53	27·8	27·5
	Mean	85·1	82·8	9·6	3·9	115·1	91·0	2·32	1·99	27·8	25·0
	SE	4·6	5·8	0·6	0·6	8·4	6·4	0·15	0·14	2·4	2·2
		NS		P<0·001		P<0·001		P<0·005		NS	
Group II											
11		63	60	20	5	120	104	1·71	1·54	27·1	25·7
12		116	85	32	9	149	100	3·33	2·31	28·7	27·2
13		58	58	16	8	98	81	1·89	2·17	32·6	37·4
14		79	66	28	14	115	86	2·10	2·05	26·6	31·1
15		69	65	14	10	88	80	2·67	1·38	38·7	21·2
16		70	77	18	8	104	66	2·72	2·36	38·8	34·2
17		76	69	15	7	118	95	2·04	1·58	26·8	22·9
18		78	76	14	8	100	80	2·82	3·09	36·0	40·7
19		66	70	15	7	100	80	1·92	1·77	29·1	25·2
20		75	72	13	10	122	104	2·55	2·58	34·0	35·8
	Mean	75·0	69·8	18·5	8·6	111·4	87·6	2·38	2·11	31·8	30·1
	SE	5·0	2·6	2·0	0·8	5·5	4·0	0·16	0·17	1·5	2·1
		NS		P<0·001		P<0·001		NS		NS	
Group III											
21		125	115	37	17	116	108	2·41	3·49	19·3	30·3
22		100	95	20	13	85	78	1·39	1·70	13·9	17·9
23		108	107	26	14	91	80	1·86	1·76	17·2	16·5
24		120	92	23	8	84	62	2·03	1·72	16·9	18·7
25		98	86	16	10	76	56	2·53	1·90	25·8	22·1
26		95	90	16	8	79	72	2·94	3·12	30·9	34·7
27		72	79	15	9	114	84	1·46	1·50	19·0	19·0
28		105	100	23	15	124	96	2·00	1·90	26·8	21·8
29		84	82	21	11	100	74	2·25	1·79	25·5	29·7
30		105	87	24	14	116	104	2·68	2·58	20·3	19·0
	Mean	101·2	93·3	22·1	11·9	98·5	81·4	2·16	2·15	21·6	23·0
	SE	4·9	3·6	2·0	1·0	5·6	5·4	0·16	0·21	1·7	2·0
		P<0·05		P<0·001		P<0·001		NS		NS	
	Mean	87·1	82·0	16·7	8·1	108·3	86·7	2·28	2·08	27·1	26·0
Total	SE	3·4	2·9	1·4	0·8	3·9	3·1	0·09	0·1	1·3	1·3
		NS		P<0·001		P<0·001		P<0·05		NS	

C, control; TNG, haemodynamic measurements at time of maximum blood pressure lowering. Means ± standard error of mean (SE). P value represents difference between C and TNG as calculated by paired Student's t test. NS=not significant, i.e. P>0·05.

The haemodynamic effects of intravenous nitroglycerin reported in Table 3 and Fig. 1 were measured at the time of maximal mean arterial pressure lowering. Similar results are obtained when the haemodynamic effects in the total group of 30 patients are examined at the end of the 1- to 3-hour infusion. Mean arterial pressure was then 93·7±3·4 mmHg (12·5±0·4 kPa), left ventricular filling pressure 10·6±0·9 mmHg (1·4±0·1 kPa), heart rate 81·8±3·0 beats/min, cardiac index 2·09±0·09 litre/min per m², and stroke work index was 35·3±1·9 g m per m².

When the effects of nitroglycerin infusion were examined in each haemodynamic subgroup, based on the patients' initial left ventricular function, the following differences were apparent (Table 3):

Stroke work index (g m per m^2)		*Pressure-time per minute index (mmHg s per min)*		*Peripheral resistance index (mmHg min/litre per m^2)*	
C	*TNG*	*C*	*TNG*	*C*	*TNG*
55·3	47·9	3112	1995	39·2	36·4
49·7	34·8	2967	2428	82·4	71·9
38·8	29·9	3188	3080	51·7	52·0
39·4	28·9	3794	1577	57·6	49·4
94·7	53·9	5432	4422	63·8	47·3
35·5	27·5	3204	1906	59·1	44·6
30·9	23·1	3500	3992	55·2	73·1
67·1	32·3	2720	2179	33·6	37·0
46·8	38·4	2882	2109	38·6	34 8
39·3	34·0	2791	2320	35·6	29·2
49 8	35·1	3359	2600	51·7	47·6
6·0	3·0	2524	2964	4·8	4·7
P<0·005		P<0·01		NS	
42·4	36·7	2977	2112	70·2	67·5
51·4	37·4	4375	2618	44·7	43·3
50·5	50·9	2413	2130	51·9	37·3
44·1	40·6	4148	2468	54·8	42·0
51·6	26·5	2550	2122	33·0	58·0
55·4	28·8	2755	1725	38 2	25·1
45·6	30·5	3192	1956	57·8	60·1
52·4	52·0	3115	2558	35·5	25·9
46·3	39·1	2788	2456	52·1	45·2
67·5	64·8	3816	3089	47·8	40·3
50·7	40·7	3213	2323·4	48·6	44·5
2·3	3·8	214	124	3·6	4·4
P<0·02		P<0·001		NS	
26·3	47·4	3254	2491	48·1	30·9
13·2	18·0	1800	1901	61·2	45·9
18·3	17·5	2920	2363	48·9	45·5
16·8	14·8	2534	1518	41·4	36·0
24·9	15 6	2984	1760	30·0	29·5
29·4	34·0	2533	2160	26·9	23·1
34·0	26·6	3478	3274	78·1	56·0
29·9	22·5	3941	2774	62·0	50·5
33·9	21·4	2777	1872	44·4	41·3
38·5	43·2	3969	2843	43·3	40 3
26·5	26·1	3019	2296	48·4	39·9
2·6	3·7	212	176	4·9	3·2
NS		P<0·001		P<0·01	
42·3	34·0	3197	2406·5	49·6	44 0
3·1	2·2	120	120 5	2·5	2·4
NS		P<0·001		P<0·001	

(1) Mean heart rate decreased 8 beats/min in group III ($P < 0{\cdot}05$) and did not change significantly in groups I and II.

(2) Left ventricular filling pressure (LVFP) decreased 5·7 mmHg (0·8 kPa) in group I ($P < 0{\cdot}001$), primarily reflecting the lower initial LVFP of 9·6 mmHg (1·3 kPa). The average decrease in LVFP was 9·9 mmHg (1·3 kPa) ($P < 0{\cdot}001$) in group II and 10·2 mmHg (1·5 kPa) ($P < 0{\cdot}001$) in group III; initial LVFPs were 18·5 and 22·1 mmHg (2·4 and 2·9 kPa), respectively.

(3) Mean arterial pressure was lowered 24·1 mmHg (3·3 kPa) in group I ($P < 0{\cdot}001$), 23·8 mmHg (3·2 kPa) in group II ($P < 0{\cdot}001$), and 17·1 mmHg (2·3 kPa) in group III ($P < 0{\cdot}001$). There were no significant differences in blood pressure responses to nitroglycerin between the three groups by unpaired Student's t test.

(4) Cardiac index did not change significantly in either group II or III but decreased 0·33 l/min per m^2 in group I ($P < 0{\cdot}005$).

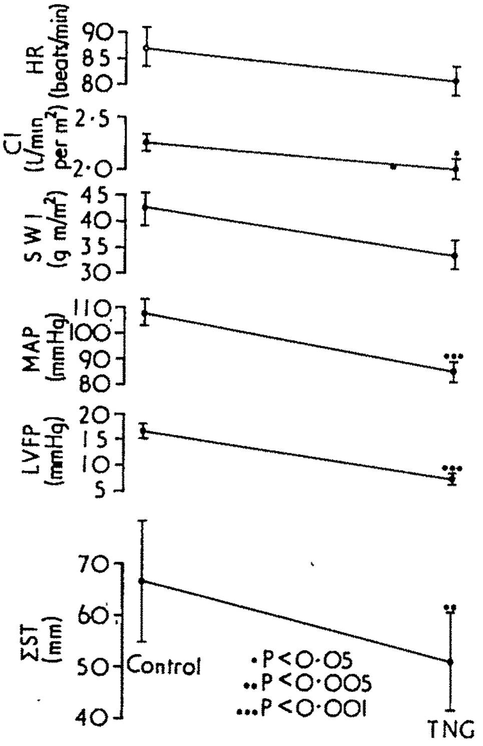

FIG. 1 *Effect of nitroglycerin infusion on haemodynamic variables (30 patients) and ΣST (15 patients). HR=heart rate, CI=cardiac index, SWI=stroke work index, MAP=mean arterial pressure, LVFP=left ventricular filling pressure, ΣST=sum of ST segment changes in 16 leads (means±standard error of mean). Control=average of two sets of measurements made before starting infusion, TNG=measurements made at maximum afterload lowering effect of nitroglycerin infusion. P values of 0·05 or less are indicated, as calculated by paired Student's t test.*

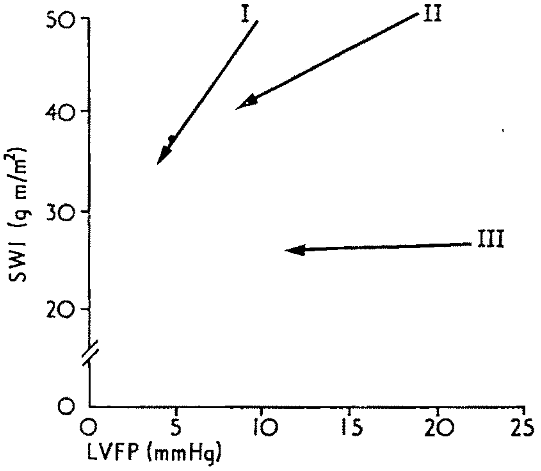

FIG. 2 *Effect of intravenous nitroglycerin on stroke work index (SWI) and left ventricular filling pressure (LVFP). Tail of each arrow is the mean control observation and arrowhead represents the values at time of maximum afterload lowering effect.*

(5) Stroke volume index did not change significantly in any of the three groups.

(6) Stroke work index, which was lowest initially (26·5 g m per m²) in group III, remained unchanged (26·1 g m per m²) during nitroglycerin infusion while both groups I and II showed significant decreases (P < 0·005 and P < 0·02, respectively). Comparison of subgroup changes in stroke work index by unpaired Student's t test revealed that the response of group III patients was significantly different from that of groups I and II (P < 0·02 and P < 0·05, respectively).

(7) Pressure-time per minute index decreased significantly in all three groups (P < 0·01, P < 0·001, and P < 0·001 for group I, II, and III, respectively).

(8) While peripheral resistance index (PRI) decreased significantly in the total group of treated patients (P < 0·001), the PRI decrease was significant only in group III (P < 0·01).

In Fig. 2 is shown graphically the haemodynamic response to nitroglycerin infusion of an average patient in each of these three haemodynamic groups. The patients in groups I and II responded with a decrease in left ventricular filling pressure and a decrease in stroke work index, while the patients in group III responded with a fall in filling pressure at the same level of stroke work. Comparison of changes in stroke volume index allows separation of changes in pressure and heart rate from changes in contractility. While changes in stroke volume index did not reach statistical significance, group I and II patients did show small decreases in stroke volume, in contrast to patients in group III who showed a small increase.

The results of the serial praecordial mapping studies in the patients receiving nitroglycerin infusion are presented in Table 4 and Fig. 1. All of the 15 nitroglycerin treated patients undergoing serial praecordial mapping studies showed a decrease in ΣST during infusion of nitroglycerin. The mean ΣST for the group decreased from 66·4±11·7 mm to 52·1±9·6 mm at the time of maximum afterload lowering effect (P < 0·005), and to 49·0±9·8 mm at the end of the infusion period (P < 0·005). This value of ΣST at the end of the infusion was not significantly different from ΣST at the time of maximum afterload lowering effect and remained significantly lower than control (P < 0·005). There was no significant change in ΣST in the one-hour period before starting the infusion.

Discussion

In our previously reported study of intravenous nitroglycerin therapy in patients with acute myocardial infarction, we showed that raised left ventricular filling pressure could be safely lowered into the normal range, with an average decrease in mean arterial pressure of only 7 mmHg (0·9 kPa) (Fla-

TABLE 4 *Effect of intravenous nitroglycerin on ΣST*

Case No.	*ΣST (mm)* *Control (1)*	*Control (2)*	*TNG (1)*	*TNG (2)*
2	24·0	22·5	18·5	18·5
3	45·5	42·5	41·5	40·0
4	89·0	98·5	55·0	57·0
7	36·5	52·0	49·5	37·0
8	66·5	37·5	24·0	16·0
11	77·5	75·0	72·0	63·0
12	130·5	131·0	127·5	129·5
15	11·5	6·0	8·0	2·5
20	182·0	175·5	139·0	139·0
22	38·5	45·0	41·5	43·0
23	63·0	66·0	45·5	45·5
24	134·5	113·0	66·0	48·0
25	27·0	32·0	20·5	20·5
29	39·0	49·5	30·5	37·0
30	66·0	50·5	43·0	38·5
Mean	68·7	66·4	52·1	49·0
SE	12·3	11·7	9·6	9·8
P value	NS	<0·005	NS	

Abbreviations: ΣST = sum of ST elevations in 16 praecordial leads. ECG standardization 1 mv = 20 mm.
Control (1) ΣST 60 minutes before infusion. Control (2) ΣST immediately before infusion. TNG (1) ΣST at maximum afterload lowering. TNG (2) ΣST at end of infusion.
SE = standard error of mean. P values represent the difference between control (1) and control (2); control (2) and TNG (1); control (2) and TNG (2); TNG (1) and TNG (2).

herty *et al.*, 1975). Thus, at the infusion rates used in the previous study (average 37 μg/min), it seemed that the venodilator action of nitroglycerin was greater than the arterial or arteriolar dilator action. With the higher infusion rates of nitroglycerin used in the present study (average 57 μg/min) a 22 mmHg (2·9 kPa) lowering of mean arterial pressure was associated with a decrease in left ventricular filling pressure comparable with that noted in the previous study. With these higher infusion rates further arterial dilator action was apparent. The extent of myocardial ischaemia, as assessed by praecordial ST mapping studies, decreased in all 15 patients with anterior myocardial infarctions in the present study despite the greater degree of arterial pressure lowering.

Because of the larger number of patients in the present study, it was possible to examine the effect of nitroglycerin therapy on left ventricular function in 3 subgroups of patients, divided according to their initial haemodynamic state. Patients with normal or only mildly impaired left ventricular function showed no improvement in ventricular performance with vasodilator therapy; a decrease in stroke work index being associated with a decrease in left ventricular filling pressure. In contrast, patients with the most severely impaired left ventricular function as indicated by both raised left ventricular filling pressures and reduced stroke work indices (< 40 g m per m^2), showed an improvement in ventricular function; in this group of patients a decrease in left ventricular filling pressure was accompanied by a maintenance of left ventricular stroke work. Since a decrease in left ventricular filling pressure is associated with a decrease in venous return, maintenance of stroke work can be interpreted as showing an improvement in left ventricular contractility.

Thus, patients with the most depressed left ventricular function (group III) received the greatest haemodynamic benefit from nitroglycerin therapy. Patients with normal or only mildly depressed left ventricular function (groups I and II), presumably not in need of an improvement in ventricular performance, nevertheless showed a reduction in ΣST. In all the groups of patients the decreased oxygen demand indicated by the fall in pressure-time per minute index may move the myocardial oxygen supply-demand imbalance somewhat nearer equilibrium, and might in this way explain the observed reduction in extent of myocardial ischaemia. Confirmation of a reduction in the extent of ischaemia by ST segment mapping studies is important since in animal studies hypotension induced by haemorrhage has been shown to result in an increase in the extent of myocardial ischaemia when assessed by ST segment mapping (Smith *et al.*, 1973).

The exact mechanism or mechanisms by which intravenous nitroglycerin reduces myocardial ischaemia despite a reduction in systemic arterial and therefore coronary perfusion pressure remains uncertain. The decrease in left ventricular filling pressure noted in the present study is probably a result of peripheral venous dilatation (Mason and Braunwald, 1965). The resulting decrease in venous return would result in a decrease in left ventricular end diastolic volume and intramyocardial wall tension and thus a decrease in myocardial oxygen consumption (Williams, Glick, and Braunwald, 1965). The decrease in mean arterial pressure, caused by peripheral arterial dilatation, would be expected to decrease myocardial wall tension further and also to result in an improvement in left ventricular function (Tsakiris *et al.*, 1968). The improvement in ΣST, might, therefore, be explained best by the reduction of both end diastolic volume and systolic pressure, with the resultant additive reduction in left ventricular wall tension, a primary determinant of oxygen consumption.

Nitroglycerin might also result in a redistribution of coronary blood flow to more ischaemic subendocardial regions as was suggested by the animal studies of Becker, Fortuin, and Pitt (1971). Smith *et al.* (1973) have furthermore shown in dogs with experimental myocardial infarction that when phenylephrine or methoxamine is added to nitroglycerin in a dose sufficient to restore arterial pressure to control levels, the beneficial effects of nitroglycerin on ΣST persisted or were in fact enhanced, suggesting a direct effect of nitroglycerin on the coronary circulation, possibly by enhancing collateral flow.

The mechanism by which intravenous nitroglycerin improves left ventricular function is also uncertain. The response of patients with severe left ventricular failure suggests an improvement in left ventricular contractility with a leftward shift to another Starling curve, while the response of those patients with normal or only midly depressed left ventricular function suggests a leftward shift down the same Starling curve. These latter two groups of patients are probably showing a decrease in left ventricular preload resulting from peripheral venous pooling, though in the absence of a measure of left ventricular volume one could not with certainty exclude changes in left ventricular compliance. The haemodynamic response of patients to nitroglycerin therapy could also be interpreted a showing an increase in left ventricular compliance; a reduction in stiffness could at least in part explain the reductions of left ventricular filling pressures noted.

The haemodynamic effects of nitroglycerin on patients with left ventricular failure complicating acute myocardial infarction appear to differ when the drug is administered by the sublingual rather than the intravenous route (Williams, Amsterdam, and Mason, 1975). In a group of patients with left ventricular failure, comparable to the patients in group III in the present study, peripheral resistance did not decrease after sublingual administration of nitroglycerin. The authors concluded that the decrease in arterial pressure noted with nitroglycerin was secondary to the decrease in cardiac output noted and not the result of a fall in peripheral resistance. While in the present study no statistically significant change in peripheral resistance was noted when nitroglycerin was administered by the intravenous route to patients with normal left ventricular function, peripheral resistance did decrease significantly in group III patients with moderately severe left ventricular failure. Furthermore, in this same group of patients intravenous nitroglycerin produced a significant decrease in heart rate while sublingual nitroglycerin did not. The route of administration of nitroglycerin appears, therefore, to be an important determinant of at least the peripheral vascular effects when this drug is administered to patients with left ventricular failure in the setting of acute myocardial infarction.

From the present study, it is not possible to comment on whether or not there is a long-term beneficial effect of nitroglycerin therapy administered during the acute phase of a myocardial infarction. Longer infusions of nitroglycerin, and therefore more prolonged reduction in the extent of myocardial ischaemia, might potentially preserve ischaemic myocardium. Assessment of the effect of nitroglycerin therapy on infarct size will await development of new techniques for the noninvasive assessment of the extent of ischaemic damage.

In summary, intravenous nitroglycerin was administered safely with continuous haemodynamic monitoring to patients with acute myocardial infarction. Infusion of nitroglycerin improved left ventricular function and/or altered left ventricular compliance in those patients with more severe left ventricular failure. Infusion of nitroglycerin also resulted in a reduction in ΣST in all patients both with and without left ventricular failure despite a substantial lowering of mean arterial pressure, suggesting that the net effect of reduction of left ventricular afterload and of preload on the extent of myocardial ischaemia is beneficial.

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A comparison of cardiovascular effects of dobutamine and isoprenaline after open heart surgery

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In a cross-over study, the cardiovascular effects of dobutamine were assessed in 11 patients who had undergone operation for replacement of the mitral or aortic valve approximately four hours earlier. In 9 of these the effects of isoprenaline were assessed for comparison. Dose-response curves were obtained using four dose levels of dobutamine in the range 1·25–10 μg/kg per min and of isoprenaline in the range of 0·005–0·04 μg/kg per min. Both drugs produced similar dose-dependent increases in heart rate and cardiac output and a dose-dependent decrease in peripheral resistance. Mean arterial pressure was only slightly increased by either drug. The positive inotropic effect of dobutamine was confirmed, but the chronotropic effect was not significantly different from that of isoprenaline. This contrasts with the findings of previous studies, and possible reasons for this are discussed.

One of the most serious sequels of cardiac surgery is cardiovascular failure associated with low cardiac output (Dietzman *et al.*, 1969). Isoprenaline is of benefit in this situation (Harrison, Kerber, and Alderman, 1970) but its use is often limited by the development of excessive tachycardia or of ventricular arrhythmias (Beregovich *et al.*, 1971). The results of animal (McRitchie *et al.*, 1973; Tuttle, 1974; Tuttle and Mills, 1975) and clinical studies in man (Jewitt *et al.*, 1974) suggests that dobutamine, a novel sympathomimetic amine, has a lesser chronotropic effect than isoprenaline at doses equipotent in inotropic effect.

The purpose of the present clinical study was to compare the effects of dobutamine and isoprenaline on heart rate, cardiac output, and arterial pressure during the early postoperative period after heart valve replacement.

Patients and methods

Eleven patients (5 male, 6 female) aged 16 to 63 years (mean 40·1) were studied. All had undergone single valve replacement (6 aortic, 5 mitral) with either Starr-Edwards (7) or Bjork-Shiley (4) prosthesis. The effects of dobutamine and isoprenaline were compared in 9 patients, the other 2 receiving dobutamine alone. Only those patients in sinus rhythm and free of other postoperative complications requiring continuous intensive treatment were included in the study. Patients in atrial fibrillation were excluded because dobutamine is known to shorten atrioventricular conduction time (Sinno *et al.*, 1973). All were receiving intermittent positive-pressure respiration via endotracheal tube and had been sedated intravenously with diazepam and papaveretum (2·5 to 5·0 mg of each). No other drugs had been given after operation. The study took place approximately four hours after the end of the operation and other intravenous infusions were interrupted during administration of dobutamine or isoprenaline.

Heart rate was determined by auscultation for one minute. Cardiac output was measured by the indicator dilution technique. Indocyanine green (5 mg dissolved in 1 ml saline) was injected through a pulmonary artery catheter inserted at the time of operation. Blood from a cannulated radial artery was pumped through a Gilford cuvette densitometer using a Harvard pump. Post-study calibration was performed with pooled blood. Duplicate control measurements of cardiac output differed by no more than 5·5 per cent. Blood pressure was measured using a Statham P23D transducer con-

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TABLE 1 *Haemodynamic effects of dobutamine*

		Control	*1·25 µg/kg per min*	*2·5 µg/kg per min*	*5·0 µg/kg per min*	*10·0 µg/kg per min*
		n=11	n=11	n=11	n=11	n=4
Heart rate (beats/min)	Mean±SE	99·1±5·2	102·9±5·4	109·1±6·7	115·4±6·9	124·2±9·8
	Per cent	100	104	110	116	125
	P		<0·02	<0·01	<0·005	<0·005
Cardiac output (l/min)	Mean±SE	3·56±0·25	3·97±0·26	4·39±0·29	5·03±0·32	6·68±0·61
	Per cent	100	111	123	141	188
	P		<0·01	<0 001	<0·001	<0·005
Cardiac index (l/min per m²)	Mean±SE	2·19±0·14	2·41±0·15	2·69±0·15	3·10±0·18	4·04±0·38
	Per cent	100	110	123	142	184
	P		<0·01	<0·001	<0·001	<0·001
Stroke volume (ml)	Mean±SE	36·4±2·8	38·6±3·2	41·3±3·3	44·7±3·2	54·1±3·9
	Per cent	100	106	113	123	149
	P		<0·05	<0·005	<0·001	<0·025
Mean arterial pressure (mmHg)	Mean±SE	82±4	84±4	87±4	89±4	86±10
	Per cent	100	103	106	109	104
	P		NS	<0·02	<0·01	<0·01
Systolic blood pressure (mmHg)	Mean±SE	115±5	110±6	126±8	134±8	128±12
	Per cent	100	104	110	115	111
	P		NS	<0·02	<0·005	<0·01
Diastolic blood pressure (mmHg)	Mean±SE	66±4	67±3	67±3	68±4	65±9
	Per cent	100	101	100	102	98
	P		NS	NS	NS	NS
Systemic vascular resistance (units)	Mean±SE	25·0±1·5	22·1±1·5	20·7±1·4	18·4±1·2	12·8±1·1
	Per cent	100	88	83	74	51
	P		<0·025	<0·005	<0·001	<0·02

TABLE 2 *Haemodynamic effects of isoprenaline*

		Control	*0·005 µg/kg per min*	*0·01 µg/kg per min*	*0·02 µg/kg per min*	*0 04 µg/kg per min*
		n=9	n=6	n=9	n=9	n=6
Heart rate (beats/min)	Mean±SE	100·0±5·1	107·2±7·0	111·0±4·4	118·1±6·0	122·0±5·8
	Per cent	100	107	111	118	122
	P		<0·05	<0·005	<0·005	<0·001
Cardiac output (l/min)	Mean±SE	3·6±0·37	4·59±0·52	4·75±0·41	5·24±0·48	6·18±0·61
	Per cent	100	126	131	144	170
	P		<0·001	<0·001	<0·01	<0·001
Cardiac index (l/min per m²)	Mean±SE	2·18±0·23	2·77±0·32	2·85±0·25	3·15±0·29	3·69±0·37
	Per cent	100	127	131	144	169
	P		<0·005	<0·001	<0·001	<0·001
Stroke volume (ml)	Mean±SE	36·9±4·0	43 4±5·0	43·1±3·8	44·9±4·3	50·1±4·7
	Per cent	100	117	117	122	136
	P		<0·005	<0·001	<0·001	<0·01
Mean arterial pressure (mmHg)	Mean±SE	81±4	83±7	86±4	89±5	85±6
	Per cent	100	102	107	109	104
	P		NS	NS	<0·02	NS
Systolic blood pressure (mmHg)	Mean±SE	113±7	117±9	126±8	133±10	130±11
	Per cent	100	102	111	117	115
	P		NS	<0·05	<0·02	<0·005
Diastolic blood pressure (mmHg)	Mean±SE	63±4	66±6	66±3	68±4	63±6
	Per cent	100	104	104	107	99
	P		NS	NS	NS	NS
Systemic vascular resistance (units)	Mean±SE	23·5±2	19·1±2·5	19±1·7	17·9±1·71	14·6±1·9
	Per cent	100	81	81	76	62
	P		NS	<0·001	<0·001	<0 005

nected to the radial artery cannula. Peripheral resistance was calculated by dividing mean arterial pressure by cardiac output.

Following duplicate baseline measurements, cumulative dose-response curves were obtained using four infusion rates of either isoprenaline in the range 0·005 to 0·04 µg/kg body weight per minute, or dobutamine in the range 1·25 to 10 µg/kg body weight per minute. All measurements were repeated after five minutes at each dose-level and the infusion rates were then increased. Dobutamine was administered intravenously at infusion rates of 1·25, 2·5, and 5·0 µg/kg per min in 11 patients and at 10 µg/kg per min in 4 of these. In 2 patients the maximum dobutamine infusion rate of 10 µg/kg per min was maintained for 10 minutes. No difference was found between measurements made after 5 and after 10 minutes infusion, respectively. Isoprenaline was administered intravenously at infusion rates of 0·01 and 0·02 µg/kg per min in 9 patients and at 0·005 and 0·04 µg/kg per min in 6 of these. Isoprenaline and dobutamine infusions were separated by an interval of 30 minutes. Of the 9 patients who received both drugs, isoprenaline was given first in 4, dobutamine first in 5. Both drugs were dissolved in 0·9 per cent sodium chloride solution and the total volume required to deliver each drug was 45 to 50 ml.

Statistical analysis using Student's paired and unpaired t-test or analysis of covariance for significance was applied appropriately to all values obtained.

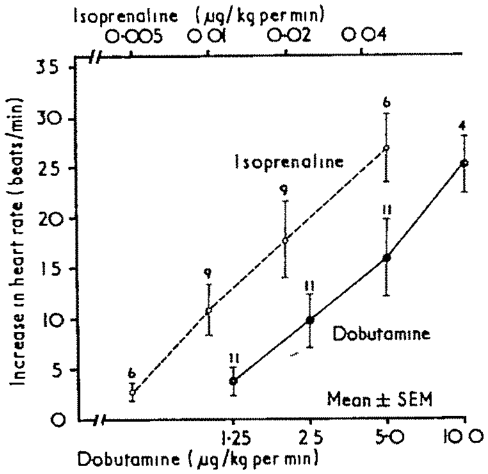

FIG. 1 *Dose related changes in heart rate (number of cases for each mean is indicated).*

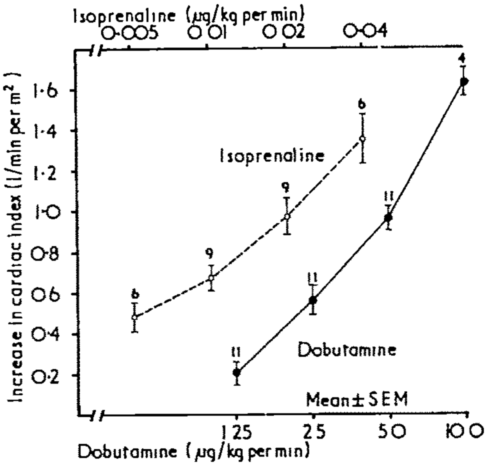

FIG. 2 *Dose related changes in cardiac index (number of cases for each mean is indicated).*

Results

The mean values for all measured and calculated parameters are shown in Tables 1 and 2. The baseline values of all parameters were approximately the same regardless of which drug was given first. The initial cardiac index was between 1·56 and 2·46 l/min per m^2 in all but one patient whose baseline value was 3·42 l/min per m^2.

Alteration in heart rate

Both drugs caused a dose-dependent increase in heart rate (Fig. 1) and the slopes were similar. Even the lowest doses produced changes significantly different from the baseline values. The maximum isoprenaline dose of 0·04 µg/kg per min produced a mean increase of 27·2±3·4 beats per minute. In the 4 patients who received the maximum dobutamine dose of 10 µg/kg per min the mean increase was 25·5±2·9 beats per minute.

Alteration in cardiac index

Both drugs caused a dose-dependent increase in cardiac index (Fig. 2). The effect of the lowest isoprenaline dose (0·48±0·07 l/min per m^2) was significantly greater ($P<0{\cdot}02$) than that of the lowest dobutamine dose (0·2±0·06 l/min per m^2). Further stepwise increase of dosage revealed no significant difference between the effects of isoprenaline and dobutamine. The maximum doses of both drugs caused increases of 1·35±0·12 (isoprenaline) and 1·62±0·07 (dobutamine) l/min per m^2.

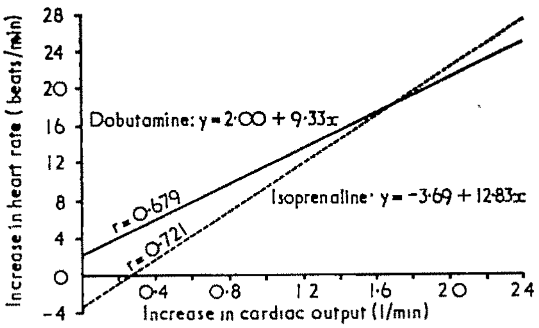

FIG. 3 *Comparison between change in heart rate and change in cardiac output. Regression lines for dobutamine (37 observations) and isoprenaline (30 observations).*

Alterations in heart rate and cardiac output compared

When alterations in heart rate were compared with alterations in cardiac output for each individual using linear regression lines (Fig. 3), analysis of covariance showed no significant difference between isoprenaline and dobutamine.

Alteration in stroke volume

The lowest dose of isoprenaline caused an increase in stroke volume of 6·3±0·9 ml/beat whereas the lowest dobutamine dose caused a significantly smaller ($P < 0 \cdot 02$) increase of 2·0±0·7 ml/beat. However, with further increase of dosage no significant difference between the effects of the two drugs could be shown.

Alteration in systemic arterial pressure and vascular resistance

Mean arterial pressure was slightly raised by both drugs. The maximal increase produced by isoprenaline was 8±2 mmHg (1·12±0·37 kPa) and this occurred at the dose level 0·02 µg/kg per min. Subsequent increase of dosage produced no further significant change. Dobutamine caused a steady dose-dependent increase of mean arterial pressure, the greatest being 9±1·5 mmHg (1·26±0·2 kPa) at the dose level of 10 µg/kg per min. A dose-dependent decrease in peripheral resistance was produced by both drugs.

Development of arrhythmias

The development of multiple ventricular ectopic beats in one patient receiving isoprenaline at 0·02 µg/kg per min precluded further infusion. Earlier infusion of dobutamine in this patient had produced no arrhythmia. Monitoring of two patients throughout the study using an electrocardiograph tape-recorder showed that occurrence of arrhythmias was not significantly different when the two drugs were compared. In one of these patients, single ventricular ectopic beats occurred as frequently before infusion of either drug as they did during the infusion periods. (These data are insufficient to permit any valid comparison between the two drugs.)

Side-effects

Apart from drug-induced arrhythmias, no side-effects were observed.

Discussion

The effects of dobutamine and isoprenaline upon heart rate, cardiac output, and blood pressure in the doses used were similar. These results alone are not sufficient to permit any firm conclusion about inotropic effect but there is other evidence to suggest that this can be inferred (Aktar, Chaudhry, and Cohn, 1973; Gunnar *et al.,* 1973; Robie *et al.,* 1974). The effect of dobutamine on cardiac output soon after open heart surgery resembles that observed by Beregovich *et al.* (1975) in patients with chronic congestive heart failure with similar low cardiac index (mean 2·1 l/min per m^2). The lesser effect of dobutamine on heart rate, suggested by previous studies (Jewitt *et al.,* 1974; McRitchie *et al.,* 1973; Tuttle, 1974; Tuttle and Mills, 1975), could not be confirmed. There are several possible reasons for this finding.

First, in our study, we observed patients early in the postoperative period after open-heart surgery when cardiac output is maximally decreased (Rastelli and Kirklin, 1966). Previous clinical studies have involved patients with only moderate impairment of cardiac function. It is possible that the response to dobutamine differed because of the severe degree of functional impairment.

Secondly, augmented sympathetic activity is the rule after open-heart surgery and in congestive cardiac failure (Dietzman *et al.,* 1969; Chidsey, Braunwald, and Morrow, 1965). Such augmentation may obscure the differential inotropic and chronotropic effects of dobutamine and isoprenaline.

Thirdly, all our patients had received intravenous papaveretum, and it is possible that concurrent administration of opiate influenced their response to dobutamine (and isoprenaline). Morphine alkaloids not only augment sympathetic activity (Hasbrouck, 1970) but also increase cardiac output and decrease peripheral resistance (Lowenstein *et al.,* 1969).

In conclusion, though previous clinical studies suggested that dobutamine had haemodynamic advantages over isoprenaline, this is not so in patients with low cardiac output after open heart surgery when such a drug should have the greatest application. This study illustrates the importance of studying the clinical pharmacology of a drug in patients for whose treatment it has been designed.

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Echocardiographic diagnosis of left atrial myxoma

Usefulness of suprasternal approach

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Three cases of left atrial myxoma were studied by echocardiography. In one case the atrial tumour was prolapsing through the mitral orifice into the left ventricular cavity; in the other two cases it was not. The angiocardiographic and operative findings correlated well with those from echocardiography. A systematic echocardiographic study is important; the suprasternal approach is useful in the echocardiographic exploration of the left atrium, especially for nonprolapsing tumours.

The value of echocardiography as a screening test in the diagnosis of atrial tumours has been well established (Wolfe, Popp, and Feigenbaum, 1969; Popp and Harrison, 1969; Kostis and Moghadam, 1970; Finegan and Harrison, 1970; Spencer, Peter, and Orgain, 1971; Waxler, Kawai, and Kasparian, 1972; Nasser *et al.*, 1972; Johnson *et al.*, 1973; Kleid *et al.*, 1973; Martinez, Giles, and Burch, 1974; Kerber, Kelly, and Gutenkauf, 1974). The need for a systematic approach in the echographic study of the mitral valve and the left atrium, for detection of abnormal clouds of echoes, has been emphasized (Nasser *et al.*, 1972; Johnson *et al.*, 1973; Martinez *et al.*, 1974). Our experience with the echographic exploration of the left atrium using the suprasternal approach in three cases of left atrial myxoma is presented as a means of improving the diagnostic accuracy of the technique.

Methods

We performed echocardiography using a Unirad Ultrasonoscope and an unfocused transducer, with a piezoelectric crystal 9·5 mm in diameter, with a primary resonant frequency of 2·25 MHz. The echocardiograms were recorded either on Polaroid film directly from the conventional oscilloscope, or on a strip chart record, with the Honeywell model 1856 fibreoptic system.

In the routine technique, the patients were studied in the supine position, with the transducer on the anterior chest wall just to the left of the sternum in the third or fourth intercostal space. The ultrasound beam was carefully manipulated until the characteristic pattern of motion of the anterior mitral valve leaflet was identified. The beam was then directed superiorly and medially until the parallel echoes of the aortic root were encountered. From this position the aortic cusps were identified by minor variations in transducer angulation, and recordings were initiated while the ultrasound beam was slowly directed inferolaterally along the main axis of the left ventricle to a point immediately distal to the mitral valve leaflets.

In the suprasternal approach, the transducer was positioned in the suprasternal notch and was directed caudad. The ultrasound beam passed through the aortic arch, right pulmonary artery, and left atrium (Fig. 1).

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Case reports

Case 1

A 30-year-old white woman was referred to Hahneman Hospital with a 5-month history of progressive dyspnoea on exertion, associated with irregular palpitation and heavy substernal pain radiating to the left arm on exertion. However, on other occasions she was completely free from symptoms. Pertinent physical findings were a blood pressure of 120/70 mmHg (160/9·3 kPa), a regular

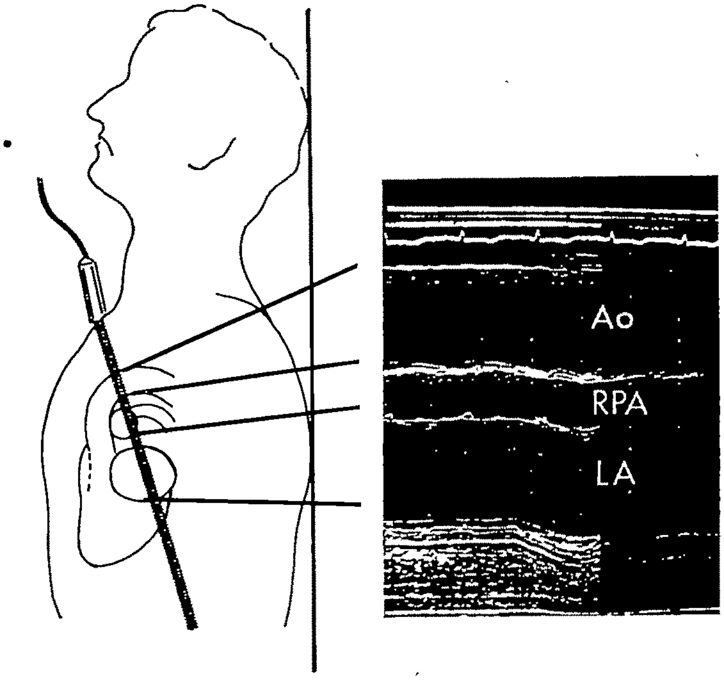

FIG. 1 *Suprasternal approach: the transducer is positioned in the suprasternal notch and directed caudad. The ultrasound beam passes through the aortic arch, right pulmonary artery, and left atrium. The suprasternal echocardiogram displayed here is the postoperative study of Case 2. Ao: aortic arch; LA: left atrium; RPA: right pulmonary artery.*

pulse of 80/min, no jugular venous distension, and clear lung fields. The heart was not enlarged; the first heart sound was loud and the second heart sound was physiologically split. An early diastolic sound, with a grade 2–3/6 diastolic murmur, was heard at the apex. There was no peripheral oedema.

The electrocardiogram was within normal limits. A chest *x*-ray film showed normal heart size and configuration, but increased vascular markings in both lung fields.

The echocardiogram (Fig. 2A) showed a cloud of echoes under the anterior mitral leaflet during diastole and a reduced diastolic slope of the mitral leaflet. The study in Fig. 2A was performed with the routine technique, with the transducer positioned in the fourth intercostal space along the left sternal border. The ultrasound beam was directed posteriorly until the anterior mitral leaflet was identified. With the transducer directed inferiorly from the suprasternal notch, the echocardiogram (Fig. 2B) shows the abnormal echo cluster in the left atrium only during systole. On angiocardiography, the size of the left atrium was at the upper limit of normal, but there was a large smooth filling defect in the left atrium near the mitral valve, moving back and forth through the mitral valve into the left ventricle. A mean diastolic gradient of 8 mmHg (1·1 kPa) was recorded across the mitral valve.

A myxomatous tumour was found in the left atrium at operation and was removed.

Case 2

A 37-year-old black woman was referred to Jackson Memorial Hospital in Miami, with a four-week history of atrial fibrillation, congestive heart failure, and persistent cough. She was not improving clinically despite treatment with digitalis and diuretics. During her stay in hospital, varying auscultatory findings were noted, including a pansystolic murmur, a mitral 'honk', and a diastolic rumble.

The electrocardiogram showed atrial fibrillation and nonspecific ST-T wave abnormalities. A chest *x*-ray film showed considerable pulmonary venous congestion and a mitral configuration of the heart. The haemoglobin was 10·8 g/dl and haematocrit 32·5 per cent.

The echocardiogram did not show a cloud of echoes under the distal portion of the anterior

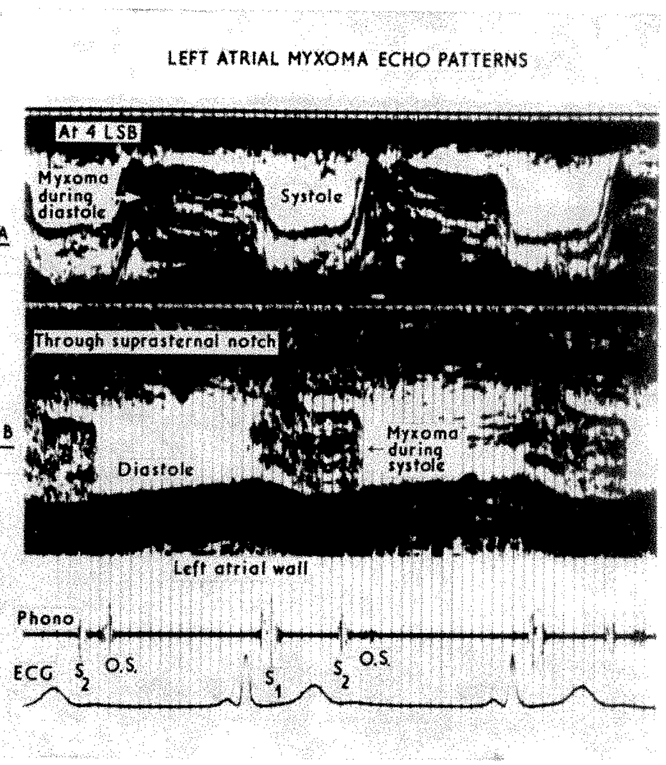

FIG. 2 *Echocardiogram of Case 1. (A) With the ultrasound beam directed posteriorly from the conventional anterior position, an abnormal cluster of echoes is produced by the myxoma behind the anterior mitral leaflet as the tumour prolapses into the left ventricle during diastole. The velocity of mitral closure during diastole is much reduced, as in mitral stenosis. (B) Echocardiogram obtained using the suprasternal approach shows the prolapsing motion of the pedunculated myxoma, which appears as a dense cluster of echoes in the left atrium during ventricular systole. Simultaneously recorded phonocardiogram and electrocardiogram are displayed below.*

mitral leaflet during diastole, but abnormal echoes did fill the entire left atrium behind the aortic root when the sound beam was directed more medially and superiorly. These abnormal echoes were clearly seen to be within the left atrial cavity when the suprasternal approach was used. They were identifiable during both ventricular systole and diastole, suggesting a failure of the tumour to enter the left ventricle.

Cardiac catheterization showed a mean diastolic gradient of 24 mmHg (3·2 kPa) across the mitral valve. The pulmonary vascular resistance was raised, and the pulmonary artery wedge pressure tracing showed a prominent *c* wave and rapid *y* descent. During angiocardiography, a large irregular mass was seen to occupy most of the cavity of the left atrium; the tumour mass appeared to move towards the mitral orifice in diastole, obliterating the orifice but not entering the left ventricular cavity; it moved back into the left atrium during systole.

These findings were confirmed at operation and the tumour was excised.

After surgical removal of the tumour repeat echocardiogram using the suprasternal approach showed that the left atrial cavity was free from abnormal echoes (Fig. 1). No abnormal echoes were detected within the left atrium and motion of the anterior mitral leaflet was normal by the conventional anterior approach.

Case 3

A 60-year-old white woman was referred to Jackson Memorial Hospital, with a history of decreasing exercise tolerance, and episodes of chest tightness and dyspnoea unrelated to physical activity, all developing over a period of 18 months.

There was also history of paroxysmal nocturnal dyspnoea and lightheadedness. Pertinent findings were a blood pressure of 150/80 mmHg (20·0/10·6 kPa) and a regular pulse of 84/min. There was no jugular venous distension. The chest was clear, and heart was not enlarged; the first heart sound was increased in intensity, and the second heart sound was physiologically split. A grade 2/6 early systolic murmur was heard at the left lower sternal border and the apex.

The electrocardiogram showed regular sinus rhythm and nonspecific ST-T wave abnormalities. The chest *x*-ray film was unremarkable.

An echocardiogram (Fig. 3A) showed that the motion of the anterior mitral leaflet was normal. No cloud of echoes was seen under the anterior mitral leaflet which moved normally during diastole. Multiple abnormal echoes were inconstantly identified behind the aortic root within the left atrium. Many of these were of extremely high intensity, suggesting calcification within a solid lesion. This seemed to move several millimetres within the left atrium but did not prolapse into the left ventricle. This finding was confirmed by echocardiograms from the suprasternal approach (Fig. 3B), with the cluster of echoes being clearly shown within the left atrium throughout the cardiac cycle. The echocardiographic study suggested a mobile atrial tumour mass, which failed to enter the left ventricle when the patient was in the supine position.

During angiocardiography, a 3×5 cm left atrial mass was seen. It occupied 70 to 80 per cent of the left atrial cavity and bounced up and down in the left atrium. It appeared to hit the atrial wall during ventricular systole and return toward the mitral orifice during diastole, but did not pass through the mitral valve orifice. The periphery of the tumour mass, easily identified during fluoroscopy, was seen to be calcified. A 5 mmHg (0·7 kPa) mean diastolic gradient was found across the mitral valve.

The findings were confirmed during operation, and the tumour was excised.

Discussion

As recently as two decades ago, atrial myxoma, the most common intracavitary tumour of the heart, was diagnosed only at necropsy or, at best, during thoracotomy. After the first successful surgical removal of an atrial myxoma in 1954 (Crafoord, 1955), the need for early preoperative diagnosis of this uncommon disorder was emphasized.

Several clinical investigators agree that atrial myxomata usually present clinically in one or more of three ways: by embolization, and/or by obstruction to blood flow, and/or by constitutional manifestations (Goodwin, 1963). The symptoms and signs, though useful in alerting the doctor to the possibility of atrial myxoma, are not diagnostic of this clinical entity which often simulates other conditions. Electrocardiography, phonocardio-

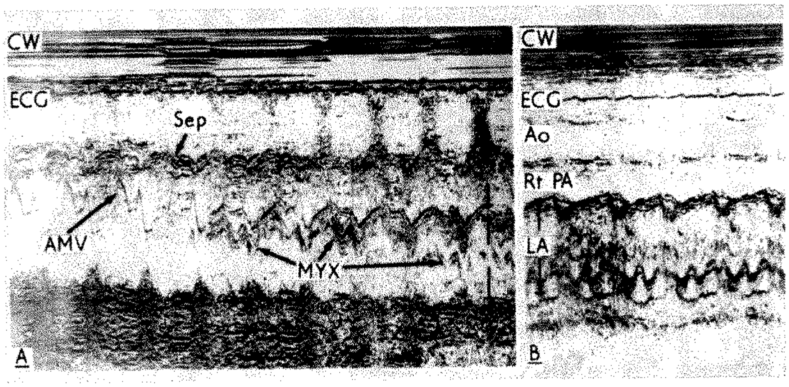

FIG. 3 *Echocardiogram of Case 3. (A) Conventional echocardiogram shows normal unobstructed motion of the anterior mitral valve leaflet during diastole. Echoes originating from the mobile but nonprolapsing myxoma within the left atrium are also present but disappear as the ultrasonic beam is directed inferiorly into the left ventricle. (B) Suprasternal approach: a cluster of echoes remaining throughout the cardiac cycle within the left atrium originates from the myxoma. Decreasing intensity settings from left to right indicate that these abnormal echoes are not technical artefacts. AMV: anterior mitral leaflet; Ao: aortic arch; CW: chest wall; ECG: electrocardiogram; LA: left atrium; MYX: myxoma; Rt PA: right pulmonary artery; Sep: interventricular septum.*

graphy, and apex cardiography may provide data suggestive of atrial tumour (Ghahramani *et al.*, 1972; Nasser *et al.*, 1972). Angiocardiography was first used in the clinical diagnosis of this disorder in 1951 (Goldberg *et al.*, 1952), and is now considered the definitive preoperative investigation, though false-positive and false-negative results occur. As a screening procedure, echocardiography is preferable to angiocardiography, which is an invasive procedure, with the risk of dislodgement of portions of left atrial myxoma, especially when the transseptal technique is used, and is also expensive and inconvenient.

The use of reflected ultrasound in the diagnosis of a left atrial tumour was first described in Germany in 1959 (Effert and Domanig). The first report in America appeared in 1968 (Schattenberg) and dealt with the value of echocardiography in differentiating between mitral stenosis and left atrial tumour. Since then several reports of successful preoperative diagnosis of left and right atrial tumours by echocardiography have appeared (Wolfe *et al.*, 1969; Popp and Harrison, 1969; Kostis and Moghadam, 1970; Finegan and Harrison, 1970; Spencer *et al.*, 1971; Waxler *et al.*, 1972; Nasser *et al.*, 1972; Johnson *et al.*, 1973; Kleid *et al.*, 1973; Martinez *et al.*, 1974; Kerber *et al.*, 1974). This technique, which is simple, noninvasive, and easily reproducible, has become popular as a screening test for atrial tumours. A mass or cloud of echoes under the anterior mitral valve leaflet during ventricular diastole is now considered diagnostic of left atrial tumour, and similarly a mass of echoes under the tricuspid leaflet is diagnostic of right atrial tumour. The diastolic slope of the anterior mitral leaflet is reduced, as in mitral stenosis, because the valve is held open by the tumour. These echocardiographic signs suggest a pedunculated atrial tumour, prolapsing through the mitral orifice into the left ventricular cavity during diastole and returning to the left atrium during ventricular systole (Nasser *et al.*, 1972; Johnson *et al.*, 1973).

Most atrial myxomata are pedunculated and traverse the atrioventricular orifice during diastole (Greenwood, 1968). However, the routine echocardiographic technique for the study of the mitral valve, placing the transducer in the fourth intercostal space along the left sternal border with the beam directed posteriorly, may fail to detect those atrial tumours which do not traverse the atrioventricular orifice. In such cases, exploration of the left atrium by ultrasound may reveal a mass of echoes within the left atrial cavity (Nasser *et al.*, 1972). Johnson *et al.* (1973) have stressed the importance of examining the mitral valve from many different angles. They reported the echocardiographic features of a left atrial myxoma which was attached to the superior left atrial wall instead of having the usual attachment to the interatrial septum; the diagnostic mass of echoes was recorded when the ultrasound beam was directed more laterally and inferiorly but was not seen when the beam was directed in the usual manner through the anterior mitral leaflet. Martinez *et al.* (1974) suggested that to arrive at a reliable echocardiographic diagnosis echoes must be obtained in at least three directions: (1) through both leaflets of the mitral valve and left ventricle; (2) through the aorta and left atrium; and (3) in an intermediate direction, through the anterior leaflet of the mitral valve and left atrium; the authors observed that this echo was difficult to record unless the left atrium was enlarged.

In this report, we describe three cases of atrial myxoma in which the echocardiogram was particularly helpful as a screening test. The suprasternal approach was used in all three cases, and in two of these was crucial. The first case is a classic example of a pedunculated left atrial tumour prolapsing through the mitral orifice into the left ventricular cavity during diastole and returning to the left atrium during systole. The characteristic cloud of echoes under the anterior mitral leaflet was readily seen during the study of the mitral valve using the standard technique. The second and third cases are examples of left atrial tumours that did not prolapse through the mitral orifice into the left ventricular cavity in diastole. A false-negative echo cardiographic study could have been obtained if the mitral valve alone had been studied. In both cases the echographic exploration of the left atrial *cavity* was extremely important in detecting the atrial tumours; the approach to the left atrial cavity with the ultrasound beam directed through the aortic root was used in these cases, but we found the suprasternal approach especially useful in exploring the left atrium for these abnormal masses. In this technique, described by Goldberg (1971), the transducer is positioned in the suprasternal notch and the ultrasound beam is directed caudad, traversing the aortic arch, the right pulmonary artery, and the left atrium. In our second and third cases, we readily identified abnormal clouds of echoes originating within the left atrial cavity. Echocardiographic exploration of the left atrial cavity either behind the aortic root using the conventional anterior approach, or by the suprasternal approach, may also be helpful in differentiating atrial tumours from severe calcific mitral stenosis when multiple echoes are often seen in the area of the anterior mitral leaflet in diastole.

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Left anterior descending coronary artery obstruction

Clinical, electrocardiographic, and angiographic correlates

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Seventy-six patients with severe (greater than 80%) occlusive left anterior descending coronary artery disease by coronary angiography were examined for the electrocardiographic characteristics of this disease in the presence (group A 59 patients) or the absence (group B 17 patients) of anterior wall asynergy (akinesis or dyskinesis). The incidence of clinically documented anterior myocardial infarction in these two groups of patients was examined. The collateral circulation to the left anterior descending coronary artery was also examined in the groups of patients with and without anterior wall asynergy. Thirty-eight of 59 (64%) patients with anterior wall asynergy (group A) showed electrocardiographic signs of anterior myocardial infarction, 17 per cent showed probable electrocardiographic signs of anterior myocardial infarction and 19 per cent showed no electrocardiographic signs. None of the 17 patients without anterior wall asynergy (group B) showed electrocardiographic signs of anterior myocardial infarction. In group A 74·6 per cent had documented clinical evidence of previous anterior myocardial infarction, whereas in group B none had clinical evidence of previous anterior myocardial infarction. Collateral filling of the distal left anterior descending coronary artery was seen in 71 per cent of group A and 100 per cent of group B patients. There was a significantly higher incidence ($P=0·02$) of collateral filling in the patients without electrocardiographic evidence of definite anterior myocardial infarction (93% of 28 patients), than in those who showed definite electrocardiographic evidence of anterior myocardial infarction (66% of 38 patients).

It is concluded that severe occlusive left anterior descending coronary artery disease with anterior wall myocardial asynergy is usually associated with electrocardiographic signs of anterior myocardial infarction, whereas equally severe left anterior descending coronary artery disease without anterior wall asynergy is rarely associated with electrocardiographic abnormalities of anterior myocardial infarction. Severe left anterior descending coronary artery obstruction without electrocardiographic and angiographic evidence of anterior myocardial infarction is usually associated with collateral circulation to the left anterior descending coronary artery and collateral circulation to the left anterior descending coronary artery is present less frequently when obstruction is associated with anterior myocardial infarction.

The theoretical and empirical basis for the association between abnormal Q waves and myocardial scars has been well established (Wilson *et al.*, 1933; Pardee, 1930; Fenichel and Kugell, 1931; Myers, Klein, and Hiratzka, 1949; Goldberger, 1945). Several investigators have looked at the classical QRS electrocardiographic abnormalities and attempted to correlate these with the presence, site, or extent of myocardial scar formation or coronary artery disease at necropsy (Horan, Flowers, and Johnson, 1971; Myers, Klein, and Stofer, 1948) or at angiography (Hilsenrath *et al.*, 1972; Friesinger and Smith, 1972; Hamby, Gupta, and Young, 1973; Williams *et al.*, 1973; Bodenheimer, Banks, and Helfant, 1975; Miller *et al.*, 1974), with varying results. In individual patients the resting electrocardiogram appears to be an inaccurate predictor of the extent of coronary artery disease unless classical transmural myocardial infarction changes

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are present (Benchimol *et al.*, 1973). Pathological Q waves on the electrocardiogram correlate very closely with localized asynergy on left ventricular cineangiography (Williams *et al.*, 1973; Miller *et al.*, 1974). This appears to be true, especially with anterior myocardial infarction as opposed to inferior wall myocardial infarction (Williams *et al.*, 1973; Miller *et al.*, 1974).

We have previously reported on the correlation of inferior wall myocardial infarction with the presence and extent of pathological Q waves in leads II, III, and aVF in patients with high grade obstructions of the right coronary artery (Shettigar *et al.*, 1974). It is the purpose of this study to: (1) evaluate electrocardiographic abnormalities associated with complete or severe obstruction of the left anterior descending coronary artery in patients with or without associated anterior wall asynergy; (2) study the incidence of clinically documented anterior myocardial infarction in these two groups of patients; and (3) examine the possible role of coronary collaterals to the left anterior descending coronary artery.

Methods

The coronary arteriograms and left ventricular cineangiograms of all patients who underwent these studies during the last three years at Palo Alto V.A. Hospital were reviewed. All patients who had significant disease (greater than 80% obstruction) of the left anterior descending coronary artery were selected for this study. Excluded were those patients who had had previous cardiac surgery or a left bundle-branch block pattern on the electrocardiogram, and those on whom inadequate clinical data were available, or cineangiograms were inadequate for interpretation because of atrial fibrillation or ventricular premature beats. Patients with congestive heart failure were also excluded. All patients included had disabling but stable angina pectoris and were considered to be candidates for saphenous vein aortocoronary bypass surgery. Coronary arteriography was usually done by the Judkins technique (Judkins, 1967) but in a few cases the Sones technique was used (Sones and Shirley, 1962). Multiple views of each coronary artery were obtained. Two subtotal (>80%) occlusions in close proximity or a subtotal and a total occlusion in close proximity or a long segment of narrowing have been considered as a single lesion. Nitroglycerin was not routinely used to enhance collateral vessel visualization. Collateral visualization of the left anterior descending coronary artery was graded as either present (left anterior descending coronary artery distal to the obstruction well visualized and at least of the calibre required for saphenous vein aortocoronary bypass surgery) or absent (no or only poor collateral filling of the left anterior descending coronary artery distal to the obstruction). All left ventricular cineangiograms were done during held inspiration in the right anterior oblique position, and usually 10 to 15 minutes after the coronary arteriograms. A careful inspection was made of any localized contraction abnormalities (Herman *et al.*, 1967) over the anterior or apical areas of the left ventricle by two independent observers with good agreement in all cases. Only definite localized akinetic or dyskinetic left ventricular wall motion was considered as asynergy in this study. If the contraction abnormality was localized to the apex without involvement of the anterior wall and there was an associated contraction abnormality over the diaphragmatic area, the patient was excluded from the study since conceivably an obstruction of the right coronary artery with a long posterior descending branch could give a contraction abnormality of the apical and diaphragmatic surface. None of the patients who showed left ventricular anterior wall asynergy experienced angina pectoris during left ventricular angiography. In one patient a satisfactory left ventricular cineangiogram was not obtained; in this patient scarring over the left ventricular anterior wall was found at the time of surgery.

Seventy-six patients with total or severe occlusive disease of the left anterior descending coronary artery met our criteria and were included in the study. They were subdivided into two groups: Group A showed definite localized anterior wall asynergy on left ventricular angiography. Group B showed no anterior wall asynergy.

The electrocardiograms, recorded within 5 days of the angiograms, were then examined for evidence of healed anterior wall myocardial infarction using the following criteria:

(1) Definite anterior wall myocardial infarction: Q waves (greater than 0·04 s duration) or QS deflections in (a) V1 to V2 or V4—anteroseptal wall myocardial infarction; (b) V2 or V3 to V4—strictly anterior wall myocardial infarction; (c) V3 or V4 to V6—anterolateral wall myocardial infarction.

(2) Possible anterior wall myocardial infarction: (a) poor R wave progression across the praecordium (V1 to V6); (b) progressive decrease in the R wave across the praecordium (V1 to V5); (c) small Q waves, less than 0·04 s duration (V2 to V4 or V5).

The incidence of previous anterior myocardial infarction was examined in the two groups of patients. The diagnosis of previous anterior

TABLE 1 *Angiographic findings in 76 patients with left anterior descending coronary artery obstruction*

Groups	*No. with left ant. desc. coron. art. disease*	*No. with 2-vessel disease*	*No. with 3-vessel disease*	*Previous anterior myocardial infarction documented in hospital*
A	59	27	18	44
B	17	5	9	0
Total No.	76	32	27	44

Group A = Anterior wall asynergy present.
Group B = Anterior wall asynergy absent.

TABLE 2 *Distribution of coronary arterial lesions in 76 patients with left anterior descending coronary artery obstruction*

Lesions in left anterior descending coronary artery				
Degree of narrowing	*Group*	*Proximal*	*Middle*	*Distal*
100%	A	39	5	2
	B	13	2	1
Between 80% and 100%	A	11	2	–
	B	1	–	–
Lesions in other coronary arteries of greater than 80% obstruction:				
Group	*Right coronary*	*Left circumflex*		*Left main*
A	46	33		2
B	12	9		2

myocardial infarction was made on the basis of a clear history of myocardial infarction accompanied by typical acute electrocardiographic changes and a rise in serum enzymes.

Results

Table 1 shows the clinical profile of our 76 patients. They were all men, ranging in age from 26 to 66 years, with a mean of 49 years. Table 2 shows the results of coronary arteriography. As can be seen, 62 patients (81·6%) had 100 per cent obstruction of the left anterior descending coronary artery, usually in the proximal third, while 14 patients (18·4%) had a subtotal obstruction (greater than 80%). Associated disease of the right coronary artery was noted in 58 patients, of the left circumflex in 42 patients, and of the left main coronary artery in 4 patients. Of 59 patients in group A, 44 (74·6%) had history, electrocardiographic, and laboratory evidence of anterior wall myocardial infarction.

The electrocardiographic changes are summarized in Table 3. In group A 38 patients (64%) show changes of a definite and 10 patients (17%) of a possible myocardial infarction over the anterior wall. In 19 per cent of group A patients and 100 per cent of group B patients there were no electrocardiographic changes of a previous myocardial infarction.

Good collateral filling of the distal left anterior descending was noted in 100 per cent of group B patients (Table 4). In group A 66 per cent of those with a definite myocardial infarction, 80 per cent of those with a possible myocardial infarction, and 82 per cent of those with no myocardial infarction on electrocardiogram had collateral filling of the distal left anterior descending coronary artery. Fig. 1 and 2 illustrate the different angiographic appearances in groups A and B and correlate the coronary arteriographic findings with left ventriculography. If one looks at all of the patients with 100 per cent obstruction of the left anterior descending coronary artery (78% of group A and 94% of group B patients) it can be seen that there was collateral filling of the left anterior descending coronary artery in 80·4 per cent of group A and 100 per cent of group B patients (Table 5).

Discussion

Previous studies have attempted to correlate the various electrocardiographic changes with postmortem findings (Fenichel and Kugell, 1931; Myers *et al.*, 1949; Horan *et al.*, 1971). More recently, others have tried to correlate electrocardiographic changes with the coronary arteriographic and left ventricular angiographic changes (Hilsenrath *et al.*, 1972; Friesinger and Smith, 1972; McConahay *et al.*, 1970; Williams *et al.*, 1973; Bodenheimer *et al.*, 1975; Miller *et al.*, 1974). Usually the approach has been to start with the electrocardiogram and then to examine the postmortem or arteriographic findings. The approach in this study is somewhat different and is similar to that of Hamby *et al.* (1973) in selecting patients for the study on arteriographic criteria and then looking for clinical and electrocardiographic correlates. Several investigations have shown good correlation between scar formation over the left ventricular anterior wall at necropsy or anterior or apical left ventricular asynergy on left ventricular cineangiography and either pathological Q waves over various combinations of leads V1 to V6 (Horan *et al.*, 1971; Williams *et al.*, 1973; Bodenheimer *et al.*, 1975; Miller *et al.*, 1974) or significant left anterior descending coronary artery disease (Williams *et al.*, 1973).

Our patients generally had severe coronary artery disease with an average of 2·4 severe lesions (80% or greater) per patient (Table 2). Many patients had associated inferior wall infarction. The effect of these associated coronary lesions and inferior wall myocardial infarctions on the electrocardiographic changes of anterior wall myocardial infarction is not known but must be considered. Of note, however, is the fact that the electrocardiographic pattern in V1 to V6 in 10 patients with isolated left anterior descending coronary artery disease and no inferior infarction did not differ significantly from those with associated coronary artery disease or inferior infarction.

The resting electrocardiogram has been found to be a poor predictor of the extent of coronary artery disease (Benchimol *et al.*, 1973). Most workers have found that in patients with electrocardiographic abnormalities indicating definite myocardial infarction there is good correlation between the site of coronary artery disease predicted from the electrocardiogram and the area of left ventricular asynergy (Williams *et al.*, 1973). In this study, looking at equally severe disease of the left anterior descending coronary artery, patients who showed anterior wall asynergy (group A) were much more likely to have electrocardiographic abnormalities of

TABLE 3 *Electrocardoigraphic findings in patients with left anterior descending coronary artery obstruction*

Groups	*Total*	*Anterior myocardial infarction*				
		None	*Possible*	*Definite*		
				Antero-septal	*Strictly anterior*	*Antero-lateral*
A	59	11 (19%)*	10 (17%)	22 (37%)	6 (10%)	10 (17%)
B	17	17 (100%)				

*7/11 patients had 100 per cent occlusion of the left anterior descending coronary artery.

TABLE 4 *Collateral filling of distal left anterior descending coronary artery*

Group A	*Total no.*	*No. with collateral filling*	*Per cent*	*No. without collateral filling*	*Per cent*
Electrocardiogram					
Definite MI	38	25	66	13	34
Possible MI	10	8	80	2	20
No MI	11	9	82	2	18
Total	59	42	71	17	29
Group B					
No MI	17	17	100	0	0

MI—myocardial infarction.

TABLE 5 *Collateral filling of distal left anterior descending coronary artery in patients with total left anterior descending coronary artery obstructions*

	Group A	*Collateral filling*	*Group B*	*Collateral filling*
100% occlusion				
Proximal third	39	36	13	13
Middle third	5	1	2	2
Distal third	2	0	1	1
Total	46	37 (80·4%)	16	16 (100%)

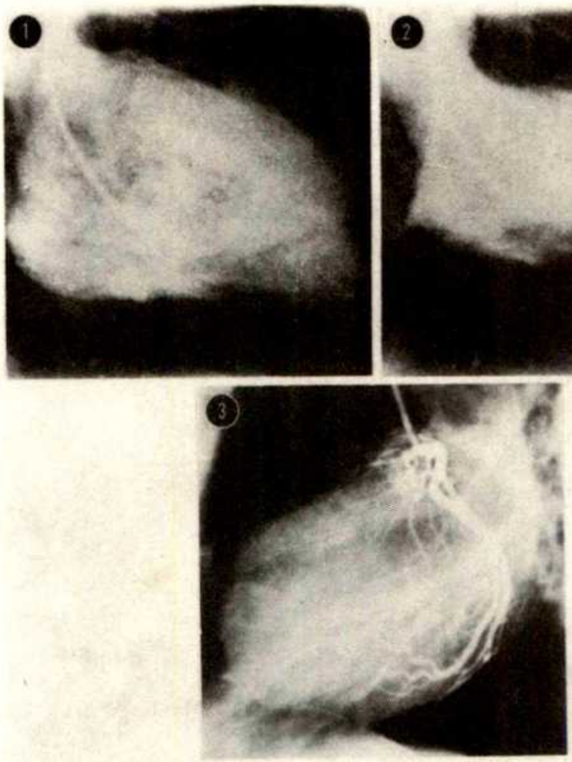

FIG. 1 *Typical example of patient from group A, showing enlarged left ventricle (1) in diastole and (2) in systole. Note extensive and severe asynergy of apical and anterior wall segments. Left coronary artery injection (3) in lateral projection, showing proximal total occlusion of left anterior descending coronary artery. No collaterals seen from either left or right coronary artery injections.*

a definite (64%) or possible (17%) myocardial infarction than patients without associated anterior wall asynergy (0%) (group B). A total of 11 patients (19%) with left ventricular anterior wall asynergy had no electrocardiographic evidence of anterior myocardial infarction. These results are in agreement with those of Miller *et al.* (1974) who found that 24 per cent of patients with left ventricular contraction abnormalities had no evidence of myocardial infarction on their electrocardiograms and with those of McConahay *et al.* (1970) who found that myocardial infarction diagnosed by electrocardiogram or vectorcardiogram is not a consistent finding in patients with ventricular contraction abnormalities. Miller *et al.* (1974), however, also included patients with hypokinesis whereas our group A patients included only those with akinesis or dyskinesis of the left ventricle. Our study also differs from previous published reports (Williams *et al.*, 1973; Bodenheimer *et al.*, 1975; Miller *et al.*, 1974) in that we have investigated the correlation between collateral circulation to the obstructed left anterior descending coronary artery and the left ventricular contraction abnormalities and electrocardiographic signs of anterior myocardial infarction. Furthermore, the incidence of clinically documented anterior myocardial infarction was investigated in both group A and B patients. Our patient population, patient selection, and methods are also slightly different.

Collateral circulation to the left anterior descending coronary artery is dependent on the absence of severe occlusive disease or thrombosis in the distal portion of the vessel. Extensive anterior myocardial infarction may be followed by thrombosis of the left anterior descending coronary artery distal to the

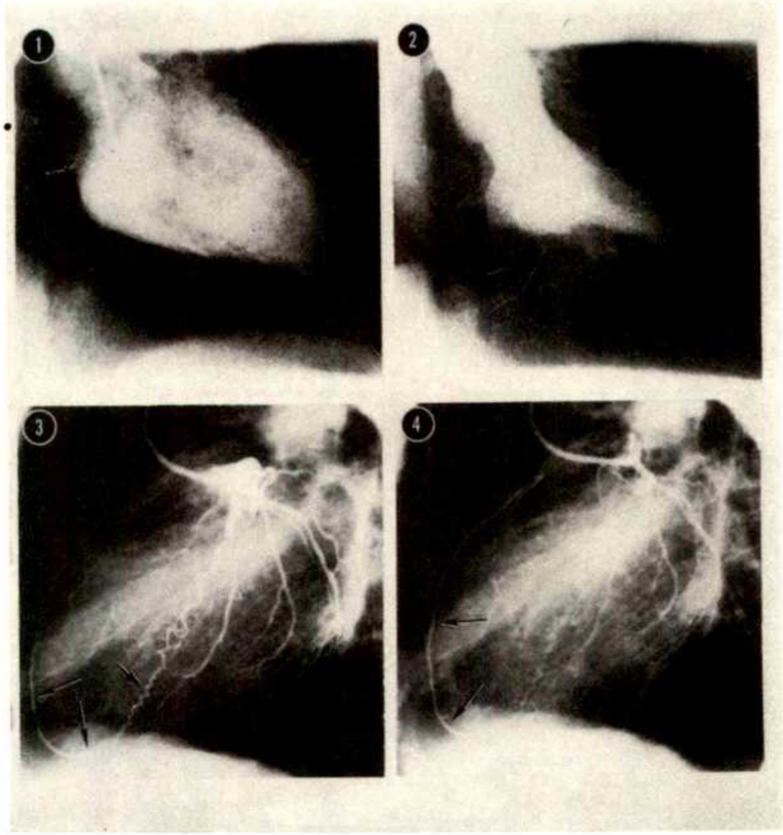

FIG. 2 *Typical group B patient showing normal left ventricular contraction (1) in diastole and (2) in systole. Coronary arteriography in lateral projection showed total proximal occlusion of left anterior descending coronary artery but with early retrograde filling via collaterals around apex (3) indicated by arrows. Later frame from same injection (4) shows excellent retrograde filling back to site of proximal stenosis.*

obstruction, and in such patients collateral filling of distal segment of the vessel does not occur; whether this is an important factor in group A patients is not known. In this study, collateral filling of the left anterior descending was noted in 71 per cent of group A patients and 100 per cent of group B patients. In the total group a significantly higher incidence (P=0·02) of collateral filling was observed in the patients who had no definite electrocardiographic signs of anterior myocardial infarction (93% of 28 patients) compared with the patients who showed electrocardiographic signs of definite anterior myocardial infarction (66% of 38 patients) (Table 4). There is disagreement on the significance of arteriographically shown coronary collaterals. Some feel that their presence is merely an expression of the severity of coronary artery disease (Hamby *et al.*, 1973; McConahay *et al.*, 1970; Miller *et al.*, 1972) and no protection against myocardial ischaemia as measured by electrocardiographic stress testing (Miller *et al.*, 1972; Helfant, Vokonas, and Gorlin, 1971). Others noted that the presence of collateral vessels in severe coronary artery disease is more likely to be associated with a normal electrocardiogram (Gensini and DaCosta, 1969), can enhance myocardial contractility in dogs (Cohen *et al.*, 1973), and can improve function in asynergic segments in the absence of Q waves in man after nitroglycerin (Banka, Bodenheimer, and Helfant, 1974), and may decrease mortality in man (Helfant *et al.*, 1971). In this study no significant difference was noted in the severity of coronary artery disease (number of arteries obstructed per patient) between group A and B patients, or between patients with and without definite electrocardiographic signs of anterior myocardial infarction. However, from the data one may conclude that the development of collateral circulation in association with left anterior descending coronary artery obstruction probably prevented the occurrence of acute anterior myocardial infarction. This conclusion is supported by animal studies (Blumgart *et al.*, 1950; Blum, Schauer, and Calef, 1938).

The effect of coronary artery dominance on the presence of anterior wall contraction abnormalities as well as on the electrocardiographic signs of anterior myocardial infarction was considered, but no significant correlation was noted. Failure to infarct and thus, failure to show anterior wall asynergy in 17 patients (group B) may in certain cases be attributed to a large posterior descending coronary artery or branches of left coronary artery supplying the territory of the left anterior descending coronary artery, especially when the latter is small. This, however, was not so in any patient in this study where most patients had severe 2- or 3-vessel disease.

In summary, in examining the significance of high grade left anterior descending coronary artery obstructions, it has been shown that left ventricular contraction abnormalities are much more likely to be associated with electrocardiographic criteria of a definite myocardial infarction. Collateral filling of the distal left anterior descending coronary artery is less frequently seen when definite myocardial infarction changes are noted on electrocardiogram and localized anterior and/or apical contraction abnormalities are seen on the left ventricular cineangiogram.

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Bipolar catheter electrograms for study of retrograde atrial activation pattern in patients without pre-excitation syndromes

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The sequence of retrograde atrial activation of premature ventricular beats was studied in 12 patients without pre-excitation syndrome. Forward and retrograde AV nodal conduction times were within normal limits. The septal low right atrial (LRA_2) deflection was inscribed 25 to 55 ms (ave: 37·9 ms) before the low left atrial (LLA_2) electrogram and 35 to 75 ms (ave: 53·7 ms) ahead of the high right atrial (HRA_2) deflection. LLA_2 preceded HRA_2 in 8 patients, more or less coincided with HRA_2 in 3 cases, and was inscribed 10 ms ahead in 1 patient. In all cases a decrease in the coupling (St_1-St_2) interval resulted in a proportional increase of the septal LRA_1-LRA_2, LLA_1-LLA_2, and HRA_1-HRA_2 intervals. Atrial echoes occurring in 3 cases had a sequence of arrival of excitation at the recording sites which was similar to the ones shown by the same patients during ventricular pacing. This is in keeping with the existence of an upper common pathway located above the area where functional longitudinal dissociation occurred.

Thus, it is concluded that impulses emerging from the AV node in a retrograde direction reach the septal low right atrium before they activate the explored low left atrial sites, regardless as to whether they arise in the ventricles or in the atria.

There have been several reports in which the sequence of atrial activation during retrograde (VA) conduction through accessory pathways has been discussed (Latour and Puech, 1957; Torresani *et al.*, 1969, Grolleau *et al.*, 1970; Spurrell, Krikler, and Sowton, 1974b; Svenson *et al.*, 1975; Gallagher *et al.*, 1975; Tonkin *et al.*, 1975a, b). In contrast, few studies have dealt with the usefulness of right and left atrial electrograms in analysing the pattern of atrial activation of impulses reaching the atria retrogradely through the AV node in patients without pre-excitation syndrome (Nicolai *et al.*, 1970; Castellanos, Castillo, and Myerburg, 1971b; Svenson *et al.*, 1974; Gallagher *et al.*, 1975; Wu *et al.*, 1975).

Subjects and methods

The technique used in our department for analysis of the electrical activity of the His bundle and several atrial sites has been discussed previously (Castellanos *et al.*, 1971b; Agha *et al.*, 1972; Castellanos *et al.*, 1972). After explaining the procedure and obtaining consent three tripolar catheter electrodes were introduced to obtain bipolar electrograms from the vicinity of the AV node in the septal low right atrium (LRA), 1 mm and/or 11 mm apart, as recorded by the His bundle electrographic lead (HBE); from the high right atrium (HRA) close to the superior vena cava, and from the low left atrium (LLA) explored through the coronary sinus in a position from which electrical stimulation produced negative P waves in leads I, II, and III (Agha *et al.*, 1972). In 4 cases, 2 HBE leads (with interelectrode distances of 1 and 11 mm, respectively) were recorded at the same time (Fig. 1). Filtered 40–500 or 400–500 Hz intracardiac electrograms were obtained simultaneously, with at least three surface leads at a paper speed of 100 mm/s.

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The moment of arrival of excitation at the recording electrodes (considered to have occurred at the

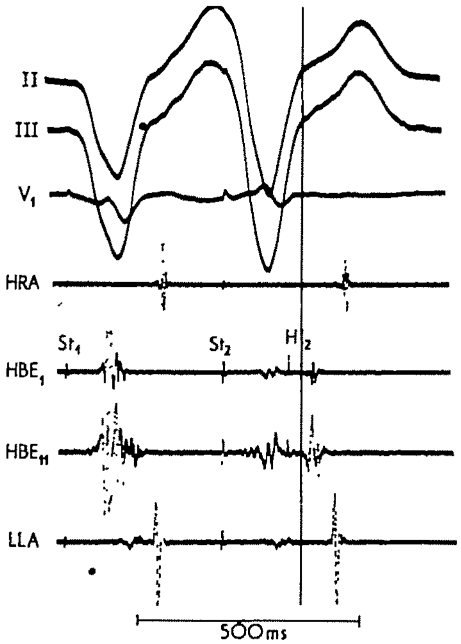

FIG. 1 *Arrival of excitation at the recording atrial sites during retrograde (VA) conduction through the AV node-His Purkinje system. HRA=high right atrium; HBE_1 and HBE_{11}=electrograms 1 and 11 mm apart recorded by the His bundle electrographic leads. LLA=low left atrium. St_1=driving stimuli. St_2=testing stimulus. The onset of the corresponding atrial electrograms was as follows: (1) low septal right atrium in HBE_1; (2) low septal right atrium in HBE_{11}; (3) LLA; and (4) HRA. This was more evident after St_2 because the corresponding deflections were farther apart from the QRS complex.*

onset of the corresponding electrograms) was studied during sinus rhythm as well as during atrial and ventricular pacing with the extrastimulus method in 12 patients with (presumably) chronic conducting disease who showed retrograde (VA) conduction during ventricular pacing. The latter was a prerequisite for this study. Retrograde activation of the atria was considered to have been present when the sinus sequence of arrival of excitation (HRA to septal LRA) changed to a septal LRA to HRA sequence. Spontaneous or induced runs of tachycardia were not seen in these patients.

Because not all retrograde His bundle and septal LRA deflections could be identified in driven beats, the time elapsing between inscription of the corresponding electrograms was measured following premature beats with coupling intervals short enough to allow the retrograde H_2 deflections to emerge after the end of the ventricular electrograms (Castillo and Castellanos, 1970).

The following nomenclature will be used in this report:

A, H, and V represent the onset of septal LRA, His bundle, and ventricular deflections in the HBE during sinus rhythm.

HRA_1, HRA_2, septal LRA_1, septal LRA_2, LLA_1-LLA_2, H_1, and H_2 are the electrograms in the corresponding sites produced by driving (St_1) and testing (St_2) impulses. HBE_1 and HBE_{11} refer to the interelectrode distances with which these leads were recorded.

Results

During sinus rhythm the duration of the AH intervals was normal according to the values presently used in our laboratory (60 to 120 ms). The sequence of arrival of excitation was from HRA to septal LRA to LLA. A similar sequence was observed when the HRA was paced.

Since this was a prerequisite in this study, retrograde (VA) conduction was seen in all patients during right ventricular apical pacing with the extrastimulus method. Retrograde AV nodal conduction time (given by the retrograde H_2-septal LRA_2 interval) was normal (between 70 and 110 ms, Table). The septal LRA_2 deflection was inscribed 25 to 55 ms (average 37·9 ms) before LLA_2 and 35 to 75 ms (average 53·7 ms) before HRA_2 (Table, Fig. 1 and 2). The LLA_2 electrogram preceded

TABLE *Differences in arrival of excitation at recording sites during retrograde atrial activation (in ms)*

Case No.	*H_2-LRA_2*	*LRA_2-LLA_2*	*LRA_2-HRA_2*	*LLA_2-HRA_2*
1	90	25	75	50
(atrial echo)	—	25	75	50
2	85	35	55	20
(atrial echo)	—	35	55	0
3	85	55	55	0
(atrial echo)	—	55	55	0
4	110	30	60	30
5	95	25	55	25
6	105	30	40	10
7	110	35	35	0
8	105	40	70	30
9	70	50	70	20
10	95	40	40	0
11	90	50	40	−10
12	85	40	50	10
Average	93·7	37 9	53·7	15·4

HRA$_2$ in 8 patients, occurred at more or less the same time in 3 patients, and was inscribed 10 ms later in 1 case. The morphology of the P waves in the standard leads could not be determined with certainty since on most occasions they appeared on top of the T waves.

In all cases a decrease in the coupling (St$_1$-St$_2$) interval was associated with an increase of the septal LRA$_1$-LRA$_2$, LLA$_1$-LLA$_2$, and HRA$_1$-HRA$_2$ intervals which was of the same order of magnitude. As mentioned previously, retrograde activation of the His bundle was seen at the shorter coupling intervals in all patients but the H$_1$-H$_2$ intervals could not be measured because H$_1$ was frequently buried within the ventricular electrogram of the HBE lead.

Although runs of tachycardia were not elicited in the patients studied, single atrial echoes were induced by premature atrial stimulation in three cases (Table). When this occurred the sequence of arrival of excitation at the recording atrial sites was similar to the one shown by the same patients during ventricular pacing (Fig. 2 and 3).

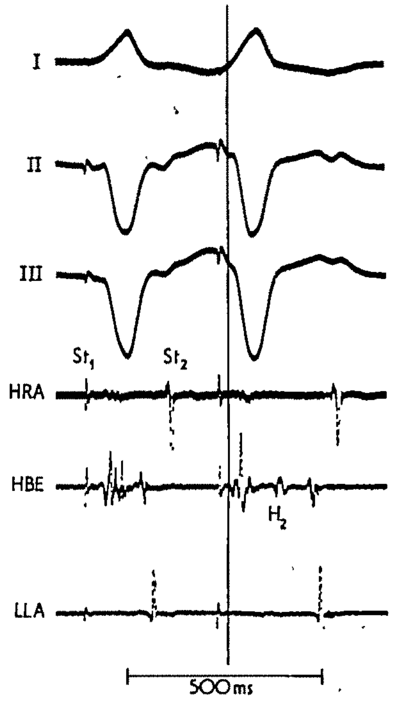

FIG. 2 *Arrival of excitation at the recording sites during retrograde (VA) conduction following driving and premature stimuli.*

Discussion

Recent studies have shown that some symptomatic patients with Wolff-Parkinson-White (WPW) syndrome might have unidirectional antegrade block in the accessory pathway, the latter being able to conduct exclusively in a retrograde direction (Slama, Coumel, and Bouvrain, 1973; Spurrell, Krikler, and Sowton, 1974a; Wellens and Durrer, 1974; Coumel and Attuel, 1974; Narula, 1974; Neuss, Schlepper, and Thormann, 1975; Svenson *et al.*, 1975; Tonkin *et al.*, 1975a, b).

Since intractable recurrent AV tachycardia can occur in these cases, surgical modes of therapy have been developed. Thus, identification of the accessory pathways which are functionally silent during antegrade conduction is of clinical importance. However, to accomplish this an understanding of the normal sequence of retrograde atrial activation is necessary.

The results of the present study show that in the absence of pre-excitation, activation of the septal LRA in the vicinity of the AV node (as recorded by the HBE lead) preceded that of the LLA (as recorded from the coronary sinus) and, of course, that of the HRA (Table, Fig. 1 and 2).

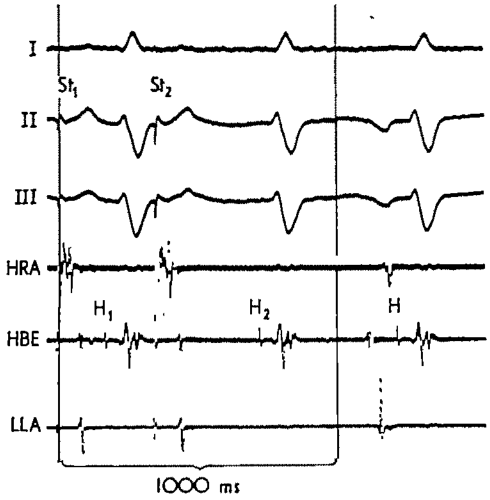

FIG. 3 *(Same patient as in Fig. 2.) Arrival of excitation at the recording sites during driving (St$_1$) and testing (St$_2$) impulses delivered to the HRA and after an (atrial) echo induced by the second atrial impulse. The sequence of retrograde atrial activation of the echo was similar to that seen in the same patient during ventricular pacing (Fig. 2).*

Moreover, in the 3 patients with atrial echo beats (elicited by premature atrial stimulation) the sequence of arrival of excitation at the recording electrodes was similar to that occurring in the same cases during the retrograde atrial activation of premature ventricular beats (Table and Fig. 2 and 3). Thus, it seems that the retrograde AV nodal-atrial pathway used by the returning impulse was the same in both situations. This is in keeping with the presence of a common 'upper pathway' located above the site where functional longitudinal dissociation of the AV node occurs (Scherf and Shookhoff, 1926; Schamroth, 1971). However, a larger number of patients should be studied to determine whether this is seen in all cases as well as in patients with accessory atrio-AV nodal or atrio-His bundle pathways.

It should be stressed that the differences in arrival of excitation at different sites are subjected to several variables that might explain the range of values shown in the Table. Foremost among these is the inevitability of some degree of catheter movement during the procedure (Agha *et al.*, 1972). Even with great care it is possible, if the procedure is prolonged or the patient is not fully co-operative, for the electrode to shift its position from the beginning to the end of the procedure. In our department this happened more often with the HRA electrode (Agha *et al.*, 1972). In retrospect, this factor might explain why in Case 11 (Table) the LLA_2 electrogram was inscribed 10 ms after that of HRA_2. Yet, the possibility of conduction through a preferential intra-atrial pathway (though less likely) cannot be completely excluded. A useful suggestion would be to compare radiographic films obtained at the beginning and at the end of the strip, which was not done in this study.

Furthermore, the coronary sinus electrode might not have been in an equivalent position in all of our cases. For instance, Tonkin *et al.* (1975b) and Svenson *et al.* (1975) have recorded several simultaneous electrograms from within the coronary sinus in patients with parietal left ventricular accessory pathways. They observed that the proximal coronary sinus to septal LRA intervals were shorter than distal coronary sinus to septal LRA intervals.

Another factor which has to be considered in evaluating differences shown in the Table is given by the method of recording electrograms as well as by the moment in which arrival of excitation at the electrodes as believed to have occurred. In some of our cases in which two HBE leads were recorded, the onset of retrograde bipolar atrial electrograms 1 mm apart occurred 15 to 20 ms after that of bipolar electrograms 11 mm apart, even when recorded simultaneously through the same catheter (Fig. 1). These differences can also be noted during sinus rhythm since the inscription of the atrial electrograms 1 mm apart occurred after that of the electrograms 11 mm apart (Fig. 4).

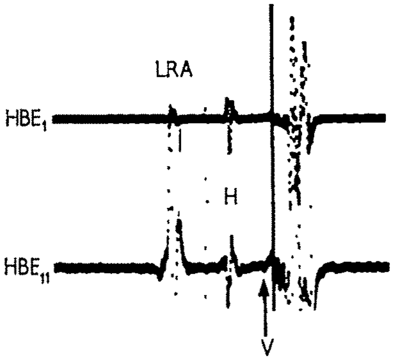

FIG. 4 *Magnification of the onset of septal low right atrial (LRA) deflections in HBE_1 and HBE_{11} during sinus rhythm. Note that the atrial electrograms recorded by the former start with the rapid deflections of the electrogram recorded with electrodes 11 mm apart. Thus, the corresponding AH interval had a shorter duration.*

That is, the AH intervals were shorter and the H_1-A_1 intervals were longer when electrodes 1 mm apart were used. This might explain why Akhtar *et al.* (1975), who used electrodes 10 mm apart, recorded shorter H_2-A_2 intervals (range 15 to 45; average 37·9 ms) than those observed in this study. However, the possibility of retrograde conduction through an antegradely blocked accessory atrio-His pathway could not be excluded in the cases of Akhtar *et al.* This raises the question as to whether patients with overt atrio-His pathways in whom both AV and VA conduction occurs via the bypass tract have a retrograde atrial activation pattern similar to that shown in Fig. 1 and 2.

In spite of this critical analysis, catheter recordings can be used to differentiate between the retrograde atrial activation pattern of impulses emerging from the AV node and that of those reaching the atria through a left sided (parietal) accessory pathway (WPW Type A). Yet, ectopic atrial impulses originating close to the area where the accessory pathway enters the left atrium could give a similar (in respect of catheter recordings) retrograde activation sequence. This can be seen in Fig. 83 of the monograph by Latour and Puech (1957) and in Fig. 6 of the article by Castellanos *et al.* (1971a).

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Case reports

British Heart Journal, 1976, **38**, 646–649.

Persistent right atrial standstill

A. Harley

From the Liverpool Regional Cardiac Centre

An asymptomatic patient with cardiomegaly caused by isolated right atrial standstill is reported. The right atrium showed no evidence of contraction on pressure records or angiographically, while the left atrium functioned normally.

Although temporary atrial standstill may result from heart disease, cardioversion, and cardiac surgery, persistent atrial standstill seems to be rare. A number of sporadic and familial cases have been reported, many associated with other heart disease or drugs. All had standstill of both atria. Persistent standstill of only one atrium in the absence of other heart disease does not appear to have been described previously.

Case report

A woman of 36 was referred for investigation of cardiomegaly associated with right bundle-branch block and a systolic murmur. She denied effort intolerance or any other symptom. The cardiomegaly had developed gradually over the previous 10 years, during which period she had had routine annual chest films taken at her place of employment. She denied any previous illness. There was no known family history of heart disease or muscular dystrophy. Clinically she appeared fit but was moderately overweight. Regular rhythm was present with a resting heart rate of 50/min. The blood pressure was 140/80 mmHg (18·6/10·6 kPa); 'a' waves were not visible in the venous pulse and were absent from a jugular venogram. No cannon waves were seen. The apical impulse was slightly displaced to the left. First and second heart sounds were normal. A soft third heart sound was audible intermittently. There was a widespread short, high pitched midsystolic murmur but no diastolic murmur. The radiological cardiothoracic ratio was 19/30·5 and the right atrium appeared to be enlarged. Over a three-month period the electrocardiogram showed a regular rhythm with very low voltage P waves, manifest only in leads III, aVL, and aVF, and right bundle-branch block. The PR interval was 0·12 s. The cycle length varied slightly as in sinus arrhythmia.

Cardiac catheterization was performed principally to exclude atrial septal defect and Ebstein's anomaly. There was no left-to-right shunt or any valvar stenosis or regurgitation. Cardiac pressures were within normal limits. The resting cardiac output was 6·6 l/min by indicator dilution. Angiographic left ventricular volume and ejection fraction, wall thickness, and left ventricular end-diastolic pressure were normal. The tricuspid valve was normally situated.

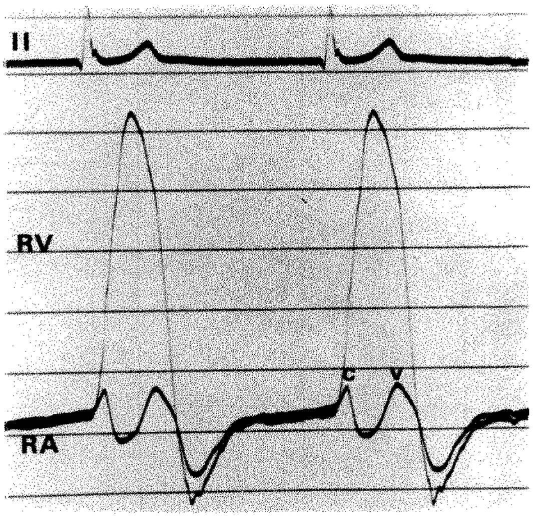

FIG. 1 *Simultaneous right atrial and ventricular pressure records using side hole catheters on each side of tricuspid valve. The 'a' wave is absent. Electromechanical interval appears longer than in Fig. 2 since both the above pressures were filtered before recording (−3dB at 5·3 Hz).*

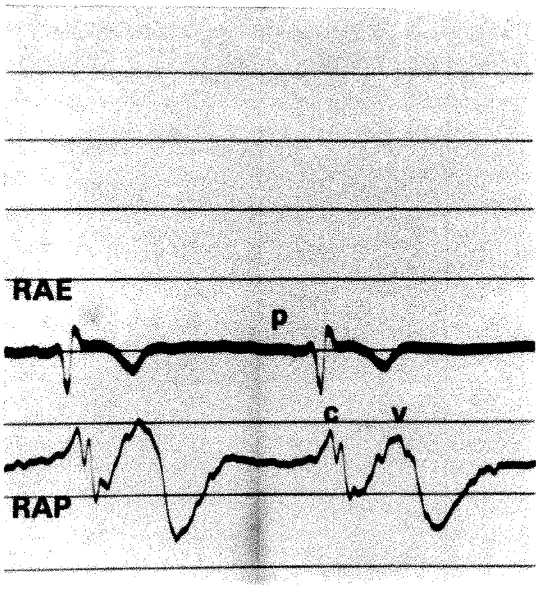

FIG. 2 *Simultaneous unfiltered right atrial pressure (RAP) and bipolar intracavitary electrogram (RAE) recorded from mid lateral right atrial wall (−3dB at 0·08 Hz and 40 Hz). The normally large atrial complex is absent. The very small wave indicated by P may represent distant left atrial activity.*

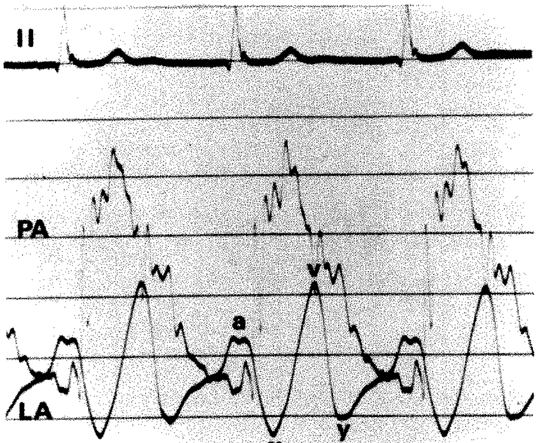

FIG. 3 *Simultaneous pulmonary arterial (PA) and direct left atrial (LA) pressure (filtered as in Fig. 1) recorded with electrocardiogram lead II. There is a normal left atrial 'a' wave beginning 0·04 s before the QRS complex.*

The right atrium showed no evidence of mechanical activity. There was no 'a' wave in the right atrial or right ventricular pressure tracings (Fig. 1). Fluoroscopy and right atrial angiography showed no right atrial contraction. Bipolar intracavitary electrograms from the mid lateral right atrial wall showed a single low amplitude biphasic complex synchronous with the right atrial 'c' wave instead of the high amplitude presystolic atrial complex normally recorded in this area (Fig. 2). Preceding this complex a very low amplitude oscillation of the baseline was just discernible (P in Fig. 2), possibly reflecting remote left atrial activity, corresponding to the low amplitude P waves in the surface electrocardiogram. In contrast, the direct left atrial pressure record (Fig. 3) showed both 'a' and 'v' waves, and left atrial contraction was visible angiographically. The right atrium was considerably enlarged while the left atrium was of normal size. The cardiomegaly appeared to be entirely the result of the right atrial enlargement. The patient remains well and requires no treatment.

Discussion

The diagnosis of right atrial standstill in this case was based on the absence of right atrial mechanical activity, absence of the normal atrial complex in the right electrogram, and isolated right atrial enlargement. There was a striking contrast between the large, motionless right atrium and the small, normally contracting left atrium when each was visualized angiographically. There was nothing to suggest other heart disease, muscular dystrophy, or any systemic disorder.

At first sight the single complex shown in the mid right electrogram in Fig. 2 suggests ventricular activation. It would, however, be difficult to distinguish this from abnormally reduced right atrial activity occurring at the same time. For this to be so, right atrial activation would have to occur about 0·1 s later than left atrial activation to explain the timing of left atrial contraction. Either right atrial electrical activity is absent, as in the case described by Patton *et al.* (1970), or there is an intra-atrial conduction defect, in which right atrial activation is delayed. This might occur if the underlying rhythm originated near the AV node or in the left atrium. However, the heart rate and phasic variations in cycle length suggested sinus rhythm rather than an ectopic atrial or AV nodal rhythm. If so, this would imply that conduction from sinus node to left atrium remained intact despite absence of right atrial activation and raises the possibility of sinoventricular conduction along the specialized conducting pathways in the right atrium, unless the AV node was activated via left atrial pathways. Interatrial block or dissociation, though uncommon, is well described (Deitz *et al.*, 1957; Cohen and Sherf, 1965). However, no mention has been found of any case with documented persistent uniatrial asystole or right atrial fibrillation in the presence of left atrial rhythm. Two of the patients reported by Rowlands, Logan, and Howitt (1967) did not develop left atrial activity after cardioversion for atrial fibrillation, when right atrial activity returned. In one case this situation was confirmed at thoracotomy. The reverse situation did not occur in their series. Rubino (1936) reported left atrial standstill with right atrial sinus rhythm in one case in response to ocular pressure.

The cause of the abnormality in this case is obscure. Right atrial standstill has been reported in patients with facioscapulohumeral dystrophy (Bloomfield and Sinclair-Smith, 1965; Caponnetto, Pastorini, and Tirelli, 1968; Baldwin *et al.*, 1973), suspected cardiac amyloid disease (Allensworth, Rice, and Lowe, 1969; Harrison and Derrick, 1969), and familial heart disease (Allensworth *et al.*, 1969; Harrison and Derrick 1969; Williams *et al.*, 1972).

Many reported cases had features of other heart disease (Rosenbaum and Levine, 1939; Magnusson, 1946; Nasi and Legnani, 1966; Jouve *et al.*, 1967; Raynaud *et al.*, 1968; Patton *et al.*, 1970), but cases without evidence of other heart disease have been reported (Wada, Takada, and Mise, 1966; Jouve *et al.*, 1967).

Of interest is the similarity between the present case and cases of idiopathic right atrial enlargement first described by Pastor and Forte (1961) and more recently reviewed by Eshaghpour, Olley, and Collins (1969). The three cases described by Pastor and Forte were not catheterized, and all had associated medical problems. In two catheterized cases (Sumner *et al.*, 1965) the right atrial electrogram, pressure, and angiogram were stated to be normal, though the specific presence of P and 'a' waves was not mentioned. The authors stated, however, that there was 'no evidence to support the existence of an abnormal sequence of activation, or contraction in the involved chamber'. Eshaghpour *et al.* (1969) illustrate a right ventricular and atrial withdrawal pressure tracing from a 6-year-old boy with idiopathic right atrial enlargement in which it is not clear whether 'a' waves are present or absent.

Possibly cases of persistent atrial standstill and idiopathic right atrial enlargement share a common pathology.

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Addendum

After this case report went to press, the patient was noted to have developed complete atrioventricular dissociation with a ventricular rate of 42/min and a left atrial rate of 56/min. The P waves were visible in the surface electrocardiogram, and in bipolar recordings from the coronary sinus.

Dissociated atrial waves were present in an apex cardiogram. In contrast, there was again no detectable mechanical or electrical activity in the right atrium. The left atrium was easily paced via the coronary sinus while there was no response to direct bipolar stimuli of up to 7 volts to the right atrial endocardium. The patient remains well with a permanent pacemaker.

Requests for reprints to Dr. Alexander Harley, Liverpool Regional Cardiac Centre, Sefton General Hospital, Smithdown Road, Liverpool L15 2HE.

British Heart Journal, 1976, **38**, 650–652.

Idiopathic aortitis with calcification of ascending aorta, and aortic and mitral valves[1]

Alan G. Rose and Robert Forman

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A young woman with unexplained radiographic calcification of the ascending aorta was found at necropsy to have healed idiopathic aortitis. Calcification also involved the aortic valve which was stenosed and the mitral valve. Death was the result of infective endocarditis of these valves with aortic ring abscess, rupture of aortic root, and cardiac tamponade.

Extensive radiographic calcification of the ascending aorta is infrequently encountered and has usually been attributed to syphilis (Higgins and Reinke, 1974). According to these authors the incidence of advanced forms of cardiovascular syphilis has decreased considerably in the past two decades, and other causes of aortic calcification now assume greater importance. In rare instances atherosclerosis (either primary or acquired on a bare area of a laceration of the aorta) may be associated with ascending aortic calcification (Levy *et al.*, 1963). Advanced atherosclerosis in elderly patients is the most frequent cause of such calcification at present (Higgins and Reinke, 1974). Two recent reports (McLoughlin *et al.*, 1974; Singleton and Merten, 1973) describe the unusual combination of extensive calcification of the ascending aorta and aortic valve in young women. The aetiology of these changes was unknown. A similar patient whose histology gives some insight into the basis for the calcification is reported.

Case report

Clinical features

The patient, a 24-year-old woman, was first seen at the age of 14 years with a history of mild spastic diplegia from childhood, and a cardiac murmur detected at the age of 8 years. She had no symptoms referable to her cardiovascular system.

Examination revealed normal peripheral pulses and a blood pressure of 145/100 mmHg (19·3/13·3 kPa) in both arms. A grade 4/6 ejection systolic murmur was heard at the base with a soft early diastolic murmur. Electrocardiogram was normal, and extensive calcification of the ascending aorta, and aortic and mitral valves was seen on radiography. Cardiac catheterization revealed a 48 mmHg (6·4 kPa) peak systolic gradient across the aortic valve which had a calculated valve area of 0·7 cm^2. The mitral valve functioned normally. Her Wassermann reaction and lupus erythematosus cell test were negative. Serum calcium, inorganic phosphate, and cholesterol were normal but total globulins were raised. The patient also suffered from psoriasis.

She remained asymptomatic over the following 10 years, with no alteration in physical signs, except that her blood pressure returned to normal. Left bundle-branch block with left axis deviation developed at the age of 15 years. She died at 24 years of age with the clinical features of infective endocarditis complicated by pericarditis.

Pathological findings

Postmortem radiography of the heart and great vessels revealed calcification of the ascending aorta together with the aortic and mitral valves (Fig. 1). The arteries arising from the aortic arch were not calcified. The aortic valve had 3 cusps which were moderately thickened and rendered immobile by extensive calcification, resulting in aortic stenosis. The commissures were not fused. The aorta showed post-stenotic dilatation. The mitral ring was heavily calcified and the cusps showed mild thickening with scanty calcification.

Infected vegetations were present on the aortic and mitral valves (Fig. 2). Cardiac tamponade had followed rupture of the aortic root through an aortic ring abscess. The latter had also interrupted the bundle of His. A coagulase positive *Staphylococcus aureus* was cultured from the infection.

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[1] Supported in part by a grant from the Chris Barnard Fund for Research in Heart Disease and Organ Transplantation.

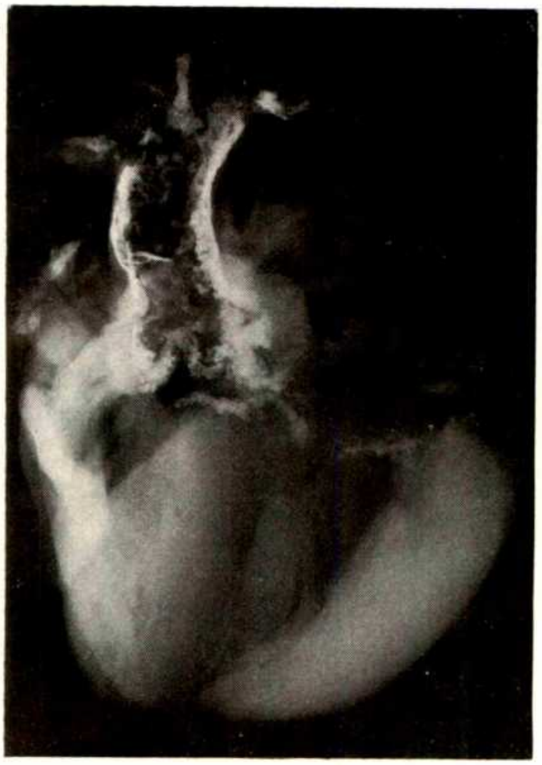

FIG. 1 *Postmortem radiograph of the heart and thoracic aorta showing calcification of the ascending aorta and left-sided heart valves.*

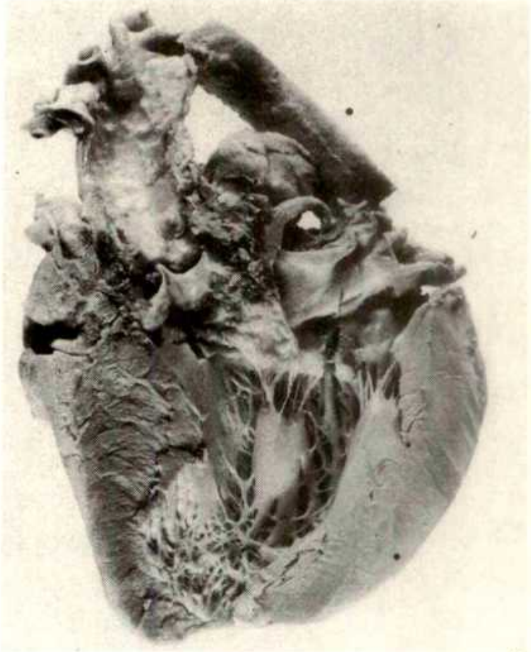

FIG. 2 *Postmortem specimen showing calcified ascending aorta and left-sided cardiac valves. Infected vegetations are present on the aortic and mitral valves.*

The pulmonary and tricuspid valves appeared normal and there were no congenital cardiac anomalies. The coronary arteries arose from narrow, calcified aortic ostia. These vessels and their epicardial branches were devoid of atheroma. The pulmonary arteries appeared normal.

Microscopical findings

The major pathology was seen in the aortic media. The ascending aorta showed severe widespread medial destruction and calcification. In most areas the media had been totally destroyed and replaced by fibrous tissue, which had become calcified. Calcification was less severe in the arch where remnants of the original media in the form of fragmented elastic fibres separated by calcified collagen were present. Calcification of zones of medial damage about 20 elastic fibres thick was seen (Fig. 3). These lesions appeared as local areas of coagulative necrosis, with shrinkage of medial components. Scanty foci of intimal fibrosis were present. Calcification was medial in distribution and atherosclerosis was not important in this regard. No inflammatory cells were present. The adventitia showed fibrous thickening.

Comment

The miscroscopical findings in the aorta were compatible with the lesions of healed idiopathic aortitis (Takayasu's disease). Calcification of the aorta may occur in idiopathic aortitis (Hachiya, 1970), in the ascending aorta, the arch, and descending aorta. The unusual feature in our case was that the calcification involved the left-sided heart valves as well as the aorta. While aortic regurgitation (often associated with hypertension) has been recorded in idiopathic aortitis (Case records of the Masachusetts General Hospital, 1961; Judge *et al.*, 1962; Schrire and Asherson, 1964), we are unaware of any reported case with aortic stenosis or calcification of mitral valve. The cause of the valvular calcification in our patient is obscure.

There are striking radiographic similarities between our patient and the two cases each reported by Singleton and Merten (1973) and McLoughlin *et al.* (1974). Both of Singleton and

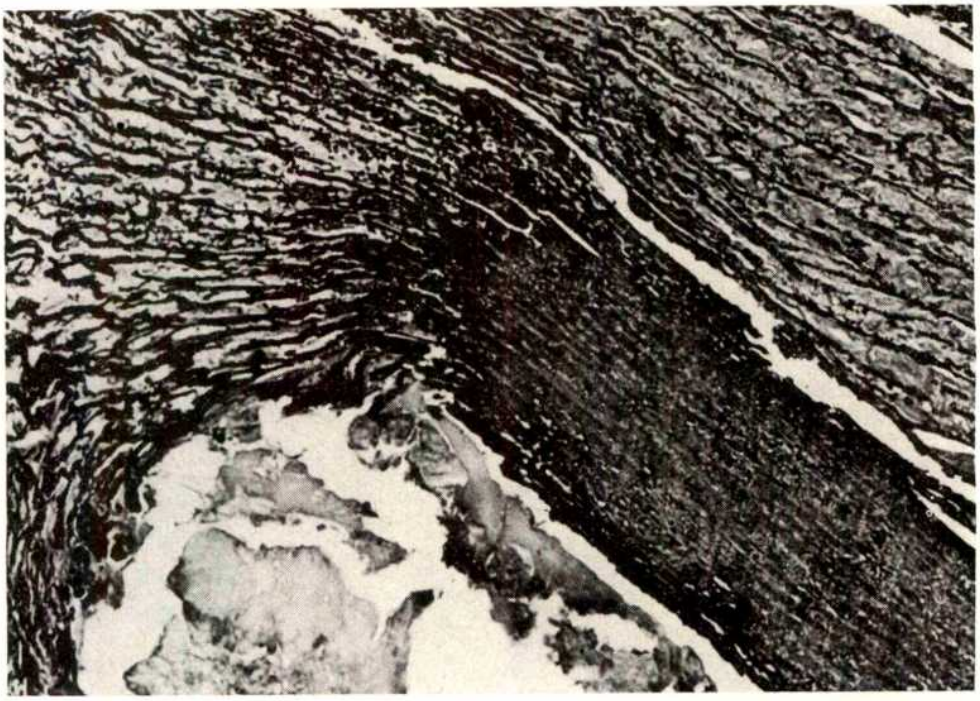

FIG. 3 *Area of coagulative necrosis of aortic media external to paler staining area of medial calcification and fragmentation. (elastic van Gieson × 115.)*

Merten's patients had calcification of the ascending aorta and aortic valve (one had scanty mitral valve calcification). The 2 patients of McLoughlin *et al.* had calcification of the aortic valve and ascending aorta. The aetiology of these changes was unknown and aortitis was not considered. These 2 patients were still alive. Both patients described by Singleton and Merten had unexplained fevers at an early age. One of them showed hyalinized degeneration of the aortic media with focal calcification and localized hyperplasia of the intima over the calcified areas. The pathology was not illustrated, but the description sounds compatible, in our view, with healed idiopathic aortitis. Our patient illustrates that in idiopathic aortitis calcification may not only involve the ascending aorta but also the aortic and mitral valves.

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Requests for reprints to Dr. Alan G. Rose, Department of Pathology, Medical School, Observatory, 7900, C.P., South Africa.

Correspondence

British Heart Journal, 1976, 38, 653–654.

Surgical treatment of acute coronary insufficiency

Sir:

In their paper 'acute coronary insufficiency—an urgent surgical condition' (*British Heart Journal*, **37**, 1053) Lawson and his colleagues state that it seemed natural to offer bypass surgery to their patients with acute coronary insufficiency because such patients appeared to have a relatively poor prognosis on medical treatment. It is implicit in their article, bearing in mind their excellent results with 41 cases, that surgery is the treatment of choice in this condition.

However, in concluding that acute coronary insufficiency has a relatively poor prognosis on medical treatment the authors base their opinions on a selective review of the literature and on papers which have defects of consistency, design, and methodology which make them unrealiable and hardly comparable guides to the natural history of the condition. They quote papers which report a high morbidity and mortality for acute coronary insufficiency during the acute stage and at long-term follow-up.

We would like to refer to other publications where the immediate and long-term outlook for these patients are very much more favourable on conservative treatment. In 1972, Krauss, Hutter, and DeSanctis reported only one death in the acute stage in 100 patients with acute coronary insufficiency. Their findings are not mentioned by the authors though their publication is alluded to in another context. In 1970 (Murnaghan, Hurley, and Mulcahy) we reported 4 deaths during the acute stage among 43 such patients (9·3%) admitted to our coronary care unit. In 1970 (Mulcahy, Murnaghan, and Hickey) we reported a 4-year mortality of 11 per cent among 52 patients with acute coronary insufficiency, but in 1975 (Mulcahy *et al.*), in a more detailed, better-designed study, we reported a 6 per cent 4-year mortality among 66 patients. All our patients were subjected to a vigorous rehabilitation, exercise, and risk factor intervention programme. If our results are confirmed by other workers, using the same conservative treatment, we shall require a very clear definition of the type of case which may benefit immediately and over the long term from bypass surgery.

It is acknowledged that we do not yet have sufficient information about the natural history of acute coronary insufficiency, whatever form of treatment is adopted (Fowler, 1971). Several pleas have been made to await properly designed randomized control trials before embarking on uncontrolled and potentially hazardous methods of treatment, whether medical or surgical (Fowler, 1971; Krauss *et al.*, 1972). With such a well-defined condition and with a large number of cases available to us, such a project should not be too difficult to undertake.

Despite the inadequate data about the natural history of acute coronary insufficiency, whatever its treatment, we feel that there may be certain subgroups of patients who may best be treated by surgical means but we believe that clear indications of treatment methods will not emerge until appropriate control trials are arranged. It is right that, as individual physicians and surgeons, we should be guided in our treatment by personal judgements but it is surely essential, from the ethical as well as the scientific points of view, that the organized medical profession should insist on proper trials before thousands of patients are subjected to unproven and possibly hazardous drugs and procedures.

Finally, in describing the results of surgical as opposed to medical treatment, we make a plea that authors should describe the exact method of medical treatment which is employed. Far too many drugs and other methods of conservative treatment are unproven and one must admit the futility of many of these.

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This letter was shown to Dr. Lawson and his colleagues who reply as follows:

Sir:

We are disappointed that Drs. Mulcahy and Hickey consider our review of the medical management of acute coronary insufficiency, as quoted in our recent paper, selective and non-representative of the natural history of the condition. We attempted, in fact, to try and survey recent British and American data as mainly assessed by cardiologists, and regret that Dr. Mulcahy's findings were not reviewed. This omission has now been rectified.

In their paper on experience of acute coronary insufficiency in a coronary care unit (Murnaghan, Hurley, and Mulcahy, 1970) they noted that 8 of 43 of these patients (18·5%) developed a myocardial infarction, 5 within 2 days and 3 within 10 days of admission. Four of these 8 (50%) were fatal. These findings are little different from the series quoted in our paper.

The 4-year follow-up studies (Mulcahy, Murnaghan, and Hickey, 1970; Mulcahy *et al.*, 1975) show encouragingly low late mortalities in patients with acute coronary insufficiency and myocardial infarcts. It is of interest that 23·5 per cent of the late deaths occurred in the first six months and 41 per cent in the first year (Mulcahy *et al.*, 1975). It is also not entirely clear in these follow-up studies whether a patient with acute coronary insufficiency who sustained a myocardial infarct was thereafter classified in the acute coronary insufficiency or myocardial infarct group. Should such a patient subsequently die, the late mortality in the two series would be affected by his classification before death. Though only one of Krauss's patients died in the acute stage, a further 21 seemed to die of cardiac causes at an average follow-up of 20 months (Krauss, Hutter, and DeSanctis, 1972).

All our patients were initially treated by bed rest, sublingual nitrate and opiate analgesics in a coronary care unit. Propranolol was rarely given and lignocaine and atropine were used only for specific arrhythmias; no other drugs were given.

We do know the value of the prospective, randomized trial. Indeed recent preliminary results in two such American trials have shown no significant difference in mortality in medically and surgically managed patients with acute coronary insufficiency, though significantly more surgically treated patients were free of angina, had higher exercise and heart rate thresholds for angina; and higher lactate extraction during tachycardia (Conti *et al.*, 1975; Seldon *et al.*, 1974). It may well be that in future, urgent surgery will be required only by the high risk groups with angina continuing for 24 to 48 hours or more after hospital admission (Gazes *et al.*, 1973; Bonchek *et al.*, 1974). All 8 patients admitted with acute coronary insufficiency and subsequently suffering a myocardial infarction (Murnaghan *et al.*, 1970) appeared to be in this category.

Our results were due to cardiological expertise in performing safe and detailed coronary arteriography, to readily available surgical skills, and to close liaison between cardiologist and surgeon. In such circumstances and given the state of the art in 1973–74, we feel that our results showed that urgent surgical treatment of acute coronary insufficiency was both safe and effective.

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Maximal exercise testing in variant angina

Sir:

The performance of exercise testing in suspected angina in order to elicit abnormal electrocardiographic patterns has always been regarded as a potentially harmful procedure, possibly aggravating or even inducing myocardial damage. Paul Wood (1956) stated 'This test is not entirely without danger and should only be carried out when . . . the resting electrocardiogram (is) normal or equivocal'. Some authorities go further and advise against this test if the resting electrocardiogram is equivocal.

Detry *et al.* (*British Heart Journal* (1975), **37,** 900) describe six cases in which the above test was performed. In Case 6 the authors comment in their table of clinical data that the resting electrocardiogram showed biphasic T waves in leads V2 and V3, and it may well be significant that they report 'Two months later he had an anteroseptal acute myocardial infarction . . .' In Case 4 (electrocardiogram not shown) they report the resting tracing as abnormal, and that during spontaneous angina 5 mm rises in the ST segments occurred in leads V1 to V3. It is surely questionable whether exercise testing was indicated (or desirable) in such a case. In the remaining four cases significant ST segment changes occurred during spontaneous angina, resting electrocardiograms being normal.

Whether or not (as the authors claim) previous reports could be wrong in 'claiming that in the variant form of angina, exercise tests were of little value . . .' there seems little doubt that the spontaneous electrocardiographic abnormalities during pain in these six cases rendered exercise electrocardiograms unnecessary and potentially dangerous.

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East Glamorgan General Hospital,
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Church Village,
Nr. Pontypridd, Glam.

Reference

Wood, P. (1956). *Diseases of the Heart and Circulation,* 2nd ed. Eyre and Spottiswoode, London.

This letter was shown to Dr. J. M. R. Detry and his co-authors who reply as follows:

Sir:

The general attitude towards exercise testing of cardiac patients varies from centre to centre, the enthusiasm of the medical staff being directly proportional to its knowledge and experience.

Our own experience is based on over 10 000 tests of maximal exercise with an incidence of 10 (1/1000) ventricular fibrillation episodes requiring ventricular defibrillation, with no death; these numbers are similar to those reported by Rochmis and Blackburn (1971) in an epidemiological survey covering 170 000 exercise tests. When the indication is well defined (exclusion of recent acute infarction) and the test adequately supervised (presence of a physician with a defibrillator), exercise testing can, therefore, be performed at a low risk; in men, the electrocardiographic data so obtained correlate well with the arteriographic findings which can be obtained only at a greater risk. In addition, exercise testing is the only way to evaluate the severity of the symptoms and to measure the physical working capacity. The presence of resting electrocardiographic abnormalities, when not related to a recent acute infarction, does not increase the risk of the procedure; such abnormalities are sometimes purely aspecific and disappear during exercise. With Bruce (1973), we consider exercise testing as the normal and necessary 'extension of the clinical examination of the ambulatory cardiac patient'; it also represents an essential step in the process of cardiac rehabilitation.

The patients with spontaneous angina pectoris represent a small percentage of the coronary patients; among them, those with spontaneous angina associated with a transient ST segment elevation constitute a small and poorly delineated group. Once the rather exceptional diagnosis of variant angina has been established, on the basis of an ST segment elevation recorded during a spontaneous attack, we agree that exercise testing is no longer a diagnostic method. It is, however, useful to evaluate the exercise tolerance of these patients, more especially as they usually have no major complaints with exercise; in our experience, the occurrence of an ST segment elevation attended by unexpected ventricular rhythm disturbances during exercise was helpful in deciding about the appropriate therapy.

J. M. R. Detry,
Ph. Mengeot, and
M. F. Rousseau,
Cardiopulmonary Laboratory,
Saint Pierre University Hospital,
Louvain, Belgium.

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Correspondence

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Anatomically corrected malposition of great arteries

Sir:

We believe that Anderson *et al.* in their descriptions and discussions of four cases of anatomically corrected malpositions of the great arteries (*British Heart Journal* (1975), **37,** 993), do not emphasize sufficiently the malpositions of the ventricles and their possible role in the genesis of a wrong aorto-pulmonary relation and a normal arterioventricular concordance, features that characterize this lesion. All four specimens presented with an anterior left ventricle and posterior right ventricle, except in Case 1 where both ventricles and arteries show side-by-side relation. The cardiac apex was always discordant in regard to the loop (mesocardia and d-loop in Case 1, laevocardia and l-loop in Case 2, dextrocardia and d-loop in Cases 3 and 4). Ventricular malposition has been described in almost all the cases reported with pathological documentation. Based also on our observations (Thiene *et al.,* 1975) we maintain that there is a morphogenetic link between malpositioned ventricles and malpositioned great arteries, and suggest that the ventricular malrotation determines anterior conus emerging from the left ventricle. The conuses are unusually twisted but the wrong torsion seem to be closely related to the malpositioned ventricles. The supposed conal inversion, therefore, does not appear 'isolated'. In other words, anatomically corrected malposition of the great arteries is often a bulboventricular malformation. The fact that the anterior left conus gives origin to the aorta instead of the pulmonary artery depends upon an abnormal truncoconal septation, but this malseptation is secondary to the conal malrotation.

Gaetano Thiene and Vincenzo Gallucci,
Istituto di Anatomia Patologica, and
Clinica Chirurgica,
Università degli Studi, Padova,
Italy.

Reference

Thiene, G., Pellegrino, P. A., Maddalena, F., and Gallucci, V. (1975). Malposizione anatomicamente corretta delle grandi arterie. *Giornale Italiano di Cardiologia,* **5,** 332.

We showed this letter to Dr. Anderson and his colleagues who reply as follows:

Sir:

We thank Drs. Thiene and Gallucci for their comments on our paper. Our aim in presenting the cases of anatomically corrected malposition was to emphasize the importance of connexion in diagnosis rather than relations (Shinebourne, Macartney, and Anderson, 1976).

In this aim we could have been more succinct in grouping both 'anatomically corrected malposition' and 'normal relations' together as 'normal connexions'. In this way we could have simplified ventriculo-arterial connexions to four categories, namely, normal connexions (concordant), transposition (discordant), double outlet ventricle, and single arterial trunk. This is as suggested by Kirklin *et al.* (1973), and we would now agree with them that anatomically corrected malposition is indeed best considered as a concordant connexion. In this way niceties regarding precise relations are avoided. Such niceties have indeed been fostered by one of us (RHA) and we accept that such arguments can be confusing and detract from the main concept (Anderson and Wilkinson, 1975; Quero-Jiménez and Raposo-Sonenfeld, 1975).

The other major point of our article on anatomically corrected malposition was that this concordant ventriculo-arterial *connexion* could exist with both atrioventricular concordance and discordance. Again, in this situation we emphasize that the connexion is of paramount importance and we are less concerned with ventricular malposition. Thus, in the cases under discussion we specifically did not state the position of the heart within the chest.

We are unable to find in our article any reference to the fact that mesocardia was present in Case 1 and dextrocardia in Case 3. Indeed, we had not observed these facts and do not believe that they can be ascertained from photographs in which the specimens were positioned to show the anatomical features at their best. We would also point out that in Cases 3 and 4 morphological left and right ventricles were not present, as we indicated in our discussion. In Case 3 we believed primitive ventricle without outlet chamber to be present; in

Case 4 we considered the ventricular morphology to be primitive ventricle with outlet chamber. In this respect it is of interest that both of the cases reported by Thiene *et al.* (1975) had tricuspid atresia and we would again interpret these specimens as having primitive ventricle with outlet chamber. We would not agree, therefore, that in all the cases the left ventricle is anterior. Furthermore, the precise mode of development of the ventricles is a controversial topic, as is the development of anatomically corrected malposition. It was for this precise reason that we did not emphasize embryogenesis in more detail. We tried to indicate that since these cases were now proven an embryological explanation was desirable. We, therefore, suggested that anatomically corrected malposition could result from conal maldevelopment together with truncal inversion (page 1012).

If we understand the concept of Drs. Thiene and Gallucci correctly we believe this also to be the concept that they are propounding. In this respect, therefore, we are in agreement. However, we would hesitate to associate these events with ventricular malposition.

Robert H. Anderson,
Cardiothoracic Institute,
Brompton Hospital, London.

Anton E. Becker,
Department of Pathology,
Wilhelmina Gasthuis,
Amsterdam.

Tom G. Losekoot,
Department of Paediatric Cardiology,
Binnen Gasthuis,
Amsterdam.

Leon M. Gerlis,
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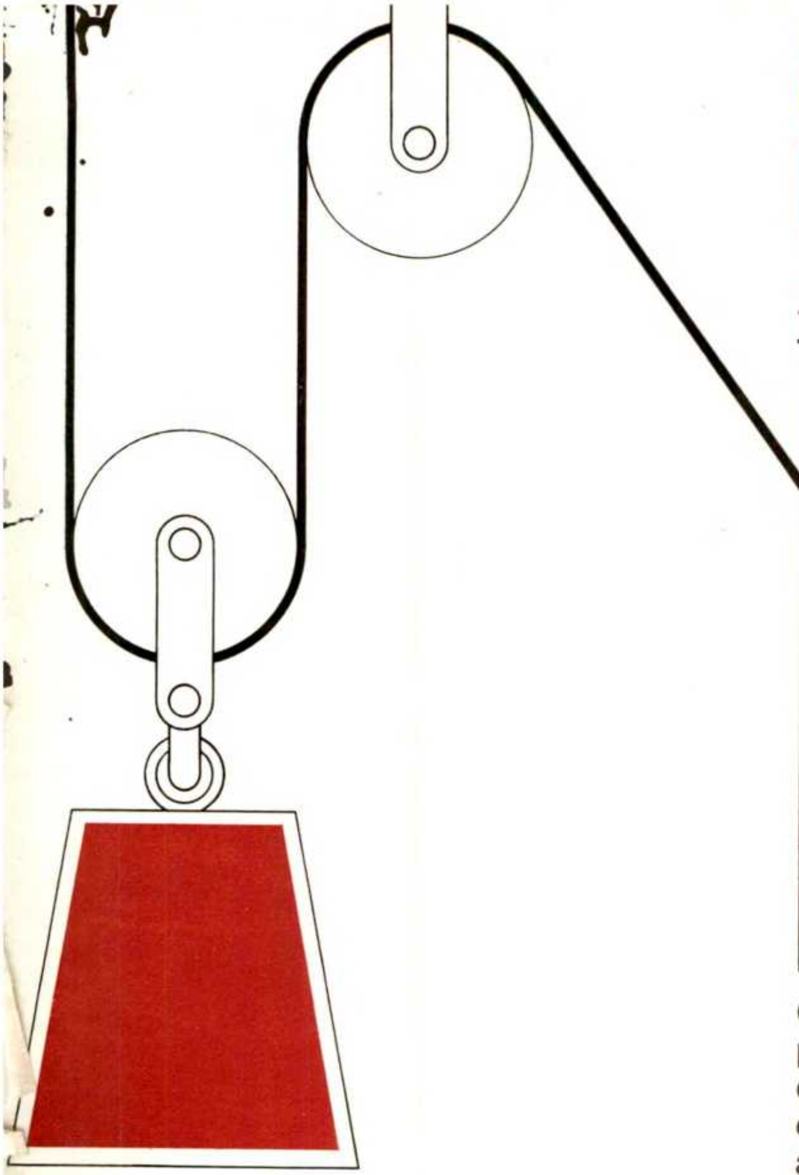

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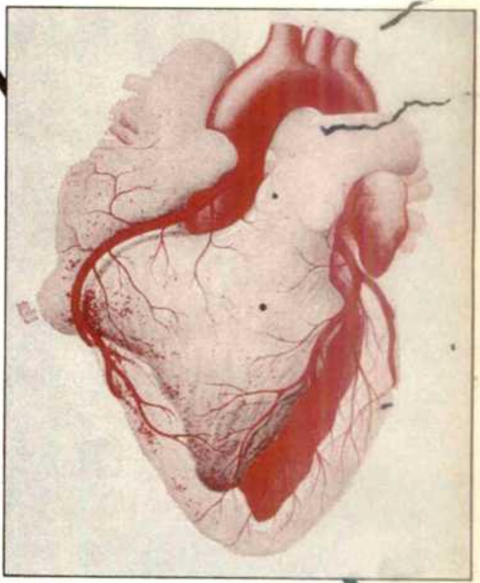

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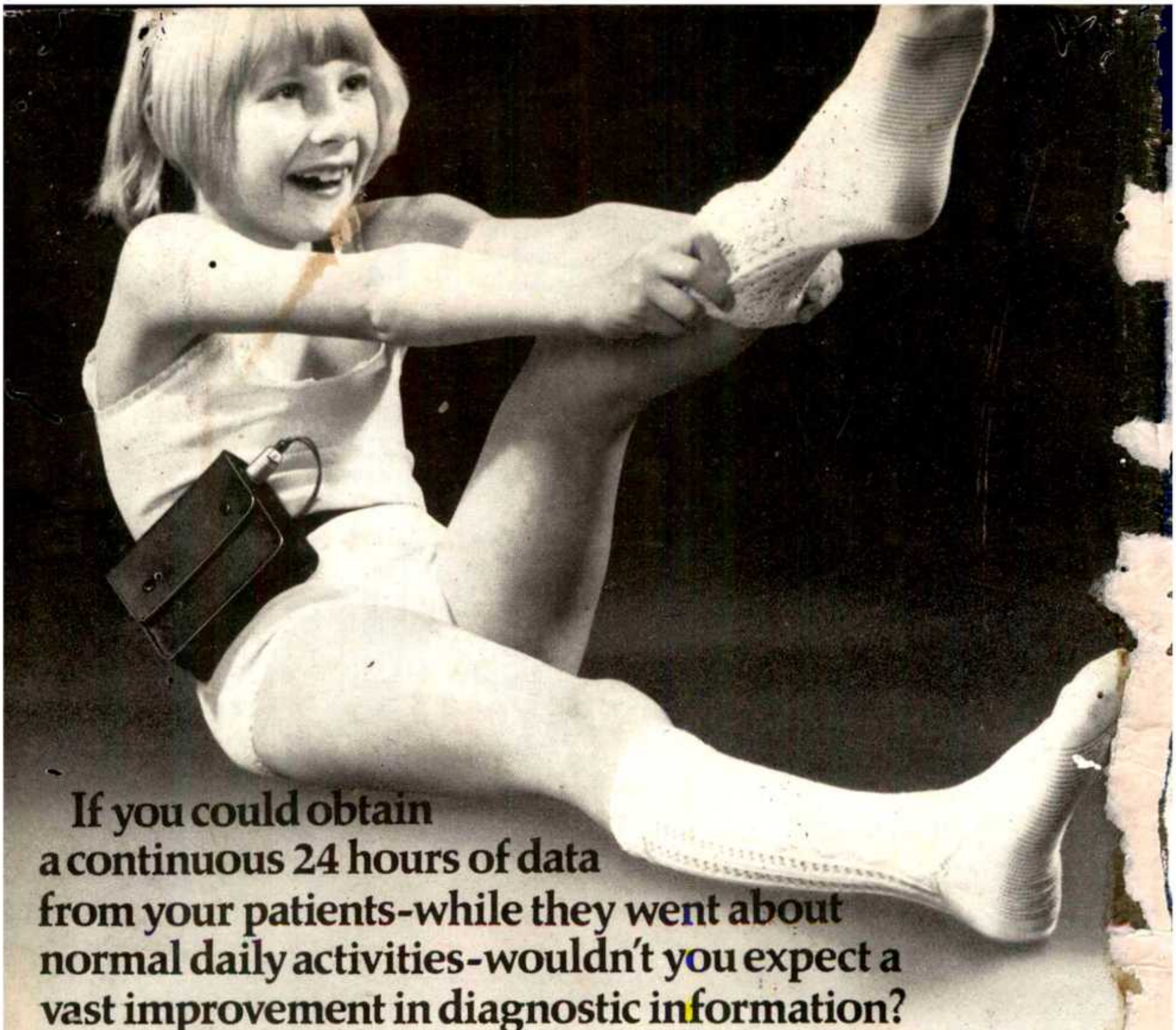

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